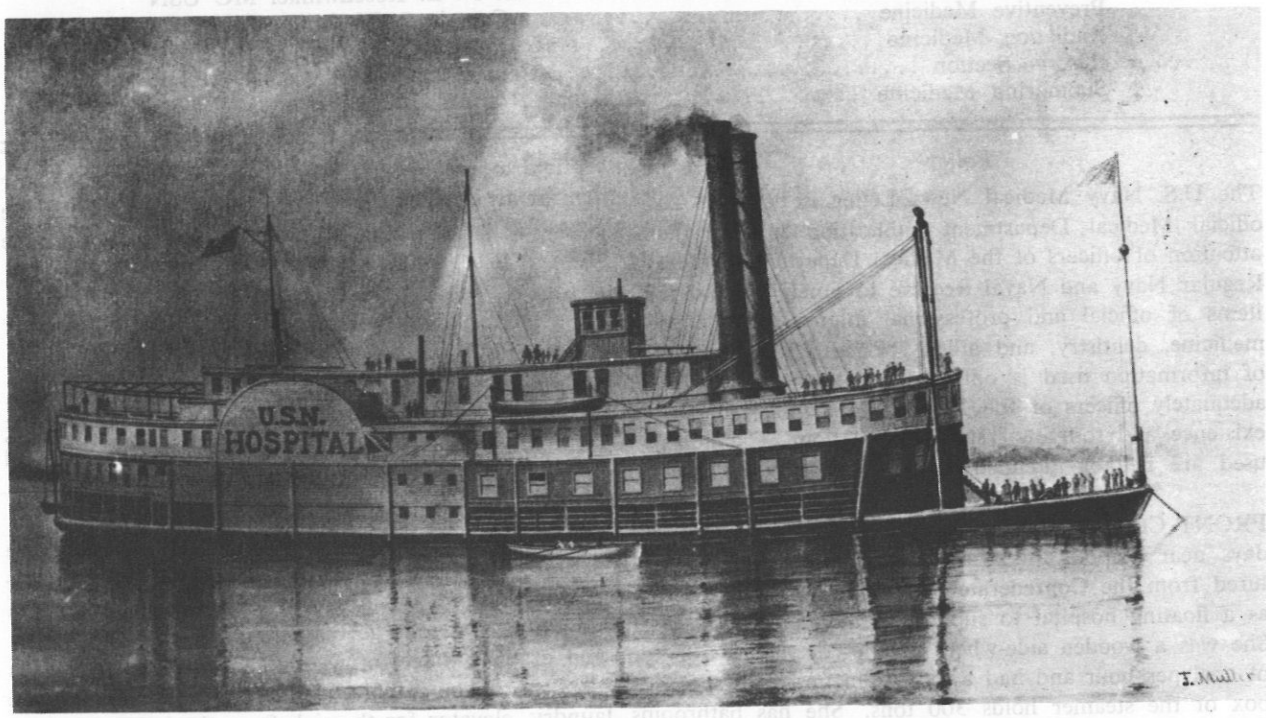
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UNITED STATES NAVY

Medical News Letter

Vol. 48 Friday, 7 October 1966 No. 7



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United States Navy
MEDICAL NEWS LETTER

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FRONT COVER: USS RED ROVER. Although another ship was used briefly as a hospital in the Barbary Pirate days near Tripoli, this was the first vessel officially commissioned as a hospital ship by the U.S. Navy. Captured from the Confederate States Navy in April 1862, she was repaired and fitted out in the next few weeks as a floating hospital to support the Union Navy's Western Flotilla. Dr. George Bixby was the Senior Surgeon. She was a wooden side-wheel steamer displacing 786 tons and drawing 8 feet of water, consumed 37½ bushels of coal per hour and had a maximum upstream speed of 9 knots. A contemporary description stated, "The ice box of the steamer holds 300 tons. She has bathrooms, laundry, elevator for the sick from the lower to upper deck, amputation room, nine different waterclosets, gauze blinds to the windows to keep the cinders and smoke from annoying the sick and well, and a regular corps of nurses." The RED ROVER received her first patient, a cholera victim, on 11 June, plus three others; 13 on the 12th, 38 on the 13th, and 37 from the gunboat MOUND CITY on the 19th. By 30 June 109 patients had been admitted; and in the next 3 months 211 patients, a total of 374 patients by the end of the year. Following formal commissioning by the Navy on 26 December 1862 several female nurses, Sisters of the Order of the Holy Cross, came aboard along with female Negro nurses who served under their direction. From December 1862 onward the new Fleet Surgeon, Ninian Pickney made the vessel his headquarters, and directed many progressive measures to improve naval medical care in the Mississippi Squadron. The RED ROVER was active during the siege of Vicksburg and related operations in mid-1863 from Memphis to New Orleans, distributing medical stores to ships of the fleet. After undergoing repairs in early 1864, she participated in patrols of the Mississippi and received patients from ships for removal to shore hospitals. From 11 December 1864 until the end of the war she was at Mound City, Illinois, having admitted during her career 2,497 patients. The RED ROVER had a crew averaging 40 men and an equal number in her medical department. She was sold at public aution 29 November 1865.

The issuance of this publication approved by the Secretary of the Navy on 4 May 1964.

THE ASSOCIATION OF CANCER AND THE NEPHROTIC SYNDROME

John C. Lee MD, H. Yamauchi MD, and James Hopper Jr. MD, San Francisco, California. *Ann Intern Med 64(1): 41–51, January 1966.*

Within recent years there has been increasing interest in malignant tumors with systemic manifestations resembling several of the auto-immune diseases. In a recent review, Greenberg, Divertie, and Woolner have summarized many of these manifestations and have stressed the possibility that the recognition of these syndromes may be an early clue to the diagnosis of cancer. The mechanism of this relationship is not understood in many instances.

An immune response of the host to components of his tumor or catabolic products therefrom has occasionally been suspected of playing an etiologic role in producing manifestations resembling dermatomyositis, chronic lymphocytic thyroiditis, rheumatoid arthritis, and other collagen diseases. Grace and Dao reported a case of dermatomyositis associated with breast carcinoma in which the patient displayed marked skin sensitivity to an extract of her own tumor. The skin and muscle manifestations tended to regress with removal of the primary tumor.

Neoplastic disease accompanied by the nephrotic syndrome has been systematically associated only with renal amyloid involvement, renal vein thrombosis, or both. Nephrosis secondary to renal amyloidosis has been associated with Hodgkin's disease, multiple myeloma, lymphosarcoma, carcinoma, and other neoplasms.

The nephrotic syndrome without renal amyloid involvement or renal vein thrombosis has not been associated with cancer, and we are not aware that an etiologic relationship has been suggested. Nesson, Sproul, Relman, and Schwartz and Johnson and Reader casually mention single cases of carcinoma of the lung associated with the nephrotic syndrome. A case of thyroid carcinoma and renal disease, a "membranous and lobular" glomerular lesion, is described in the Massachusetts General Hospital case records. Malley has seen a case with carcinomatosis thought to originate in the gallbladder in which there was glomerular basement membrane thickening compatible with a membranous lesion.

In the present paper we describe, both clinically and microscopically, renal lesions occurring in 11 adult patients in the population of the University of California Hospital and Clinics who presented with the nephrotic syndrome in a 10-year period (1953 through 1962) and at a closely related time (0 through 14 months) in the course of their illness were found to have cancer. The period 1953 through 1962 refers only to the interval during which the nephrotic syndrome became clinically apparent.

Description of Terms

A precise definition of the nephrotic syndrome presents difficulties. It is classically defined as a clinical entity characterized by massive proteinuria, hypoproteinemia (particularly involving albumin), hyperlipidemia, lipiduria, and edema. When all the classical features are present, the entity can easily be recognized. Particularly in the adult, all of these features are not always present. One may ask, in fact, how many of the features are required and to what degree they must be present.

It is obvious that in any patient population the incidence of the nephrotic syndrome will vary, depending on the definition used. The above classical definition was considered too indefinite to be adopted in the present study. Furthermore, its use would have led to a relatively low incidence in adults, since many do not demonstrate all the classic features. In our series, this would favor a higher incidence of cases of carcinoma with nephrotic syndrome.

As a starting point, we used a definition similar to Schreiner's, which emphasizes that the nephrotic syndrome is characterized by the following five parameters: (1) massive proteinuria, (2) urinary excre-

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tion of lipid, (3) variable tendency toward edema, (4) hypoalbuminemia, and (5) hyperlipemia. Like Schreiner, we specified excretion of 3.5 g or more of protein/24 hr/ 1.73 m^2 of body surface. Further requirements were serum albumin depression to 3.0 g/100 ml or less and serum cholesterol elevation to 300 mg/100 ml or more. It was also required that the values of four of the five parameters be abnormal, and always the first and fourth to the extent specified above, unless findings consistent with the nephrotic syndrome could be demonstrated by renal biopsy or autopsy. On the basis of renal tissue diagnosis, ten cases were included that otherwise would have been excluded from the series because they did not fulfill our criteria.

Our case material, then, was made up of patients with idiopathic nephrosis. Nephrosis related to diabetic glomerular sclerosis, amyloidosis, renal vein thrombosis, and other special causes were excluded from the study—at least on clinical grounds, and often by examination of renal tissue. Whenever possible, the renal lesion was judged by tissue diagnosis from renal biopsy or autopsy (Table 1). In addition to examination by light microscopy, the lesion was frequently further studied by electron microscopy, including 6 of the 11 cases of carcinoma.

Material and Methods

Selection of cases from the hospital clinical records and the surgical pathology and autopsy files was made on the basis of clincial and laboratory evidence of the nephrotic syndrome as described above (Description of Terms) or histologic evidence of membranous or lobular glomerulonephritis obtained by percutaneous renal biopsy or autopsy. During the period 1953 through 1962, 101 such cases were studied. In all but 12 cases, diagnosis was reached by method of tissue study (Table 2).

Of the 101 patients in this study, 11 had malignant neoplastic disease. Percutaneous renal biopsy was performed on 7 of these 11 patients; autopsy, on 5. Both renal biopsy and autopsy material were studied in 2 of the 11 cases. Thus renal tissue diagnosis was made in all but 1 of the 11 cases.

The expected cancer incidence in an age group similar to our group of 101 patients was ascertained in several ways. First, the New York Life Tables for rates of cancer morbidity were applied to our 101 patients by pairing according to age and sex. The expected incidence in the New York population was only 1%.

We then screened two of our own patient populations at the University of California Medical Center, attempting to pair our 101 nephrotic patients with similar sex and age groups of patients with coronary occlusion and rheumatoid arthritis (Table 3). The later group was selected because it was likely to have been followed for as long a period as the nephrotic subjects. Complete pairing could not be carried out with the coronary occlusion group since our search

TABLE 1. Renal Lesions Observed in 11 Cancer Patients, Time of Onset of Renal and Neoplastic Lesions

Patient No.	Age, Sex	Clinical Onset of Renal Lesion	Discovery of Neoplasm	Renal Lesion		Type of Neoplasm	Patient's status as of July 1, 1965	
				Biopsy	Diagnosis (Light Microscopy)			Cause of Death
1	50, F	July, 1954	July, 1954	July, 1954	Membranous glomerulonephritis	Bronchogenic† carcinoma (B)	Dead (October 1954)	Cancer
2	54, F	August, 1959	July, 1959	November, 1959*	Lipoid nephrosis	Adenocarcinoma of distal colon (B)	Alive renal lesion, "B" response‡	
3	57, M	February, 1957	December, 1957	—	Membranous glomerulonephritis	Bronchogenic carcinoma (N)	Dead (February 1958)	Cancer
4	65, F	April, 1960	November, 1961	June, 1960*	Membranous glomerulonephritis	Adenocarcinoma of ovary (B, N)	Dead (September 1962)	Cancer
5	64, F	October, 1961	November, 1961	January, 1963*	Membranous glomerulonephritis	Squamous cell carcinoma in situ, uterine cervix (B)	Renal status unknown after January 1963	
6	61, M	September, 1960	November, 1960	April, 1961*	Membranous glomerulonephritis	Basal cell carcinoma of cheek (B)	Dead (March 1962)	Renal failure
7	38, F	May, 1957	May, 1957	—	Membranous glomerulonephritis	Undifferentiated carcinoma (origin not known) (N)	Dead (May 1957)	Cancer
8	61, M	April, 1962	May, 1963	June, 1962*	Membranous glomerulonephritis	Adenocarcinoma of sigmoid colon (B)	Dead (October 1963)	Cancer
9	51, M	December, 1961	July, 1962	March, 1962*	Membranous glomerulonephritis	Squamous carcinoma of pharynx (B, N)	Dead (October 1962)	Cancer
10	52, M	March, 1960	January, 1960	—	—	Squamous cell carcinoma, floor of mouth (B)	Dead (June 1963)	Cancer
11	55, M	April, 1956	June, 1957	—	Lobular glomerulonephritis	Adenocarcinoma of kidney, monocytic leukemia (N)	Dead (June 1957)	Cancer

* Renal biopsy, electron microscopy.
† Diagnosis of neoplasm established by biopsy (B), necropsy (N), or both.
‡ See criteria of renal status according to Adams and associates.

of the records revealed only one patient under 20 years of age. Above 34 years, however, the patients could be paired. Only one case of cancer was found: carcinoma of the urinary bladder in a woman aged 50 years, occurring in the randomly selected cases of coronary occlusion. This selected group seemed to confirm the New York Life Table figure for incidence of cancer, inasmuch as the expected incidence in the portion of our population that we were unable to pair (the young age group) would be very low. In the patient population with rheumatoid arthritis, exact pairing by age and sex was accomplished, and no cases of cancer were found.

Tissue for light microscopy was routinely fixed in 10% neutral buffered formalin or 10% Zenker-formol and embedded in paraffin. Percutaneous renal biopsy material was stained with hematoxylin and eosin, Masson's trichrome, the periodic acid-Schiff reaction, and congo red. All tumor tissues were routinely studied with hematoxylin and eosin and other stains necessary for accurate diagnosis and classification.

Renal biopsy material for electron microscopy was routinely fixed in buffered 1% osmium tetroxide. Prior to 1962, methacrylate was used as embedding material; thereafter, epoxy resins. Thin sections were prepared with an LKB Ultratome and stained with lead hydroxide and uranyl acetate. Electron micrographs were taken with RCA-EMU2B or RCA-EMU3F electron microscopes.

Results

The incidence of malignant neoplasms in our group of 101 patients with the nephrotic syndrome observed during the 10-year period of study was 10.9%, well above the expected cancer incidence in this age group. The neoplasms encountered (Table 1) are those commonly found in the general adult population. There was no particular predominance of a specific tumor. Only 1 of the 11 involved the kidney or urinary tract as either the primary or metastatic site of cancer. The age incidence is similar to that in adults with neoplastic disease. Eight of the 11 patients died as a result of their neoplastic disease, and 1 died of renal failure; 2 of the 11 are alive as of July 1, 1965, without recurrence of cancer. In each of these patients, however, proteinuria has continued.

TABLE 2. Diagnosis of 101 Cases of the Nephrotic Syndrone, 1953 Through 1962

Tissue Diagnosis	Cases
	no.
By renal biopsy	75
By autopsy	14
Total:	89
(By renal biopsy and autopsy)	
None	12
	101

There was opportunity to treat only 4 of the 11 patients (Patients 2, 3, 7, and 9, Table 1) by means of glucocorticoid therapy. Two (Patients 2 and 9) made good renal responses, classed as *B* according to the criteria of Adams, Maxwell, Bernstein, and Kleeman, while two (Patients 3 and 7) made, at best, only *C* responses; both died before their neoplasms could be treated. Patient 2 continues in *B*

TABLE 3. Age-Sex Pairing of Patient Populations Studied

Age	Nephrotic Syndrome		Coronary Occlusion		Rheumatoid Arthritis	
	Male	Female	Male	Female	Male	Female
yr						
0–19	10	6	1	0	10	6
20–24	12	7	0	0	12	7
25–29	3	4	3	1	3	4
30–34	5	5	5	2	5	5
35–39	4	3*	4	3	4	3
40–44	7	5	7	5	7	5
45–49	1	3	1	3	1	3
50–54	9†	5†	9	5*	9	5
55–59	4†	0	4	0	4	0
60–64	3†	1*	3	1	3	1
65+	1	3*	1	3	1	3
Total Patients	101		61		101	

* One cancer patient.
† Two cancer patients.

status, with normal renal function, after successful removal of her neoplasm in 1959; Patient 9 died from cancer although her neoplasm was treated with radiation. Two other patients (Patients 5 and 8), followed for a comparable time, refused glucocorticoid treatment; their renal lesions continued to grow worse throughout the observation period. The other 5 patients were not treated for various reasons, including death shortly after discovery of the renal lesion and neoplasm, contraindications to glucocorticoid therapy, and loss to follow-up study. The status of the patients as of July 1, 1965 is presented in Table 1.

In 7 of the 11 patients the clinical onset of the renal lesion preceded the discovery of the neoplasm. In the case of Patient 8, this interval was 11 months; in Patient 11, 14 months. In the remaining 4 patients the renal lesion and the neoplasm were discovered coincidentally or within a year of each other (Table 1), and it was not possible to distinguish which was first.

It should be noted that none of the 11 patients were treated at any time with anti-tumor therapy of the anti-inflammatory or anti-immune type, such as 6-mercaptopurine or nitrogen mustards.* Neither radiation nor chemotherapeutic agents likely to produce a nephrotic syndrome were administered prior to the time of renal tissue diagnosis. A summary of significant laboratory data is presented in Table 4.

Light Microscopy

The renal lesion responsible for the nephrotic syndrome was lipid nephrosis in one case, membranous glomerulonephritis in nine cases, and lobular glomerulonephritis in one case. It is our impression that lobular glomerulonephritis in this particular case may represent a more advanced progression of the diffuse membranous lesion.

The one case of lipoid nephrosis was judged normal when studied by light microscopy (Figure 1, not reproduced); the characteristic changes of the disease were established only by electron microscopy. The cases of diffuse membranous glomerulonephritis were characterized by thickening of the glomerular capillary basement membrane, which tended to involve all glomeruli to a relatively uniform degree (Figure 2, not reproduced). Occasional slight increase in cellularity that tended to involve the axial portion was observed, particularly in association with arterial nephrosclerosis. The lobular glomerulonephritis was characterized by extreme nodular thickening of the glomerular capillary basement membranes along with marked proliferation and clustering of mesangial cells and axial stalk thickening (Figure 3, not reproduced). Exudative glomerular lesions were not observed.

Electron Microscopy

Pure lipoid nephrosis is characterized by a relatively normal appearing basement membrane, with fusion and increased density of the epithelial cell foot processes (Figure 4, not reproduced). This lesion was observed in only one patient (Patient 2, Table 1). Membranous glomerulonephritis, on the other hand, has marked basement membrane irregularities, and electron-dense material is deposited on the epithelial side of the basement membrane. The epithelial cell foot processes are fused and of increased density (Figure 5, not reproduced). Similar electron microscope findings have been described by others as typical of membranous glomerulonephritis.

* The idea that certain cytostatic agents, including nitrogen mustards,, can produce a membranous lesion needs re-examination in the light of the possibility that the tumor itself and not the cytostatic agent may in fact be an etiologic factor. Further, it seems contradictory that cystostatic agents have been successfully used in the treatment of membranous renal lesions and, therefore, can allegedly both produce and cure the same lesion.

TABLE 4. Summary of Laboratory Data in 11 Patients with Cancer and Nephrotic Syndrome

Patient No.	Urine Protein	Lipiduria	Serum Protein (Albumin/Globulin)	Serum Cholesterol	Creatinine Clearance
	g/24 hr		*g/100 ml*	*mg/100 ml*	*ml/min*
1	6.6	+	1.4/2.8	620	24
2	9.8	+	2.0/3.6	478	80
3	14.0	+	1.7/2.5	397	61
4	18.0	+	0.8/3.2	876	95
5	11.4	+	2.0/3.9	375	40
6	11.2	+	1.6/3.3	176	43
7	19.0	+	1.4/2.4	466	41
8	7.0	+	1.7/3.6	492	112
9	14.0	+	1.9/3.6	258	55
10	4.2	+	2.8/4.9	Not known	32
11	(++++)*	Not known	2.5/1.2	348	Not known

*++++ = qualitative test only, indicating heavy proteinuria.

Discussion

The occurrence of lipoid nephrosis and membranous glomerulonephritis in cancer patients may be more frequent than is generally realized. In the case of either lesion, the histologic appearance of the kidney with light microscopy may be deceptively normal, and the true nature of the glomerular basement membrane alterations may be appreciated only with electron microscopy. Further, although membranous glomerulonephritis is frequently accompanied by the nephrotic syndrome in adults, it need not be; there may be no apparent edema and only mild to moderate amounts of proteinuria.

The relationship of lipoid nephrosis and membranous glomerulonephritis to malignant neoplasms is not clear. It is well documented that a patient with neoplastic disease will frequently develop antibody directed toward some component of his lesion. The possibility exists that the renal lesion may reflect an immune response directed against the tumor and that the renal lesion is produced by circulating soluble antigen-antibody complex. Whatever the mechanism, the renal lesions described here were not different morphologically from lipoid nephrosis and membranous glomerulonephritis observed in patients without tumors.

There is recent evidence that lipoid nephrosis and membranous glomerulonephritis are immunologic diseases; this has been documented by a variety of techniques. It is risky to suggest a dependent relationship of one disease to another; nonetheless, the coincidental occurrence of cancer and of the membranous type of renal lesion in our series of cases is high. This has caused us to speculate that the two conditions may be related and that neoplasms may act as antigen, producing antigen-antibody complex capable of being deposited along the glomerular basement membranes.

As a result of our experience, it is suggested that any nephrotic patient of 40 years or over should be carefully and repeatedly screened for cancer.

Summary

The coincidental occurrence of cancer and the nephrotic syndrome due to lipoid nephrosis, membranous glomerulonephritis, or lobular glomerulonephritis was observed in 11 of 101 patients with nephrosis in a 10-year period of study. Cases of nephrotic syndrome due to diabetic glomerulosclerosis, amyloidosis, renal vein thrombosis, and other special causes were eliminated from the survey. The observed incidence of cancer (10.9%) was well above that expected for a similar population group.

The renal lesions observed are thought to be related to possible immune responses of the host to his neoplasm, with fixation of antigen-antibody complex to the glomerular capillary basement membrane.

Addendum

Since closing this 10-year study, we have observed three additional patients with neoplasms accompanied by renal lesions and frank nephrotic syndromes. All had renal biopsies.

The first, a 53-year-old man, had inoperable bronchogenic carcinoma and a severe membranous glomerulonephritis that did not respond to glucocorticoid treatment. The second, a 44-year-old man, had squamous cell carcinoma of the lung and a severe lesion characterized by both intensive proliferative and membranous glomerular nephritis. He was not treated with glucocorticoids because of advanced renal failure. The third, a 28-year-old woman, had the onset of membranous glomerulonephritis discovered a month after removal of a large ovarian dermoid cyst. The nephrotic syndrome persisted despite treatment with glucocorticoids, 40 mg/day, for approximately 3 months.

Acknowledgments

The authors wish to express their gratitude to Dr. Calvin Zippin and Mrs. Diana Lum, biostatisticians, General Tumor Registry, Cancer Research Institute, University of California Medical Center, San Francisco, Calif., for their helpful suggestions. They also gratefully acknowledge the assistance of Mrs. Elizabeth Weedon in searching the medical records.

The unsolicited research grant to Dr. Hopper from the San Mateo Heart Association, which can be spent in whatever way will best advance the investigator's research, is gratefully acknowledged for its promotion of the present research.

(The references and figures may be seen in the original article.)

NONMETASTATIC NEUROLOGIC SYNDROMES WITH EXTRACEREBRAL MALIGNANCIES

Desmond S. O'Doherty MD and C. Vernon Sanders MD, Georgetown University School of Medicine, Washington, D.C. *GP XXXIII(6): 96–102, June 1966.*

The association of carcinoma of the lung or other malignancies with neurologic syndromes, in the absence of metastasis to the nervous system, should be recognized. Cerebellar and peripheral nerve syndromes are most common but cerebral, spinal cord and muscular syndromes also occur. One plausible explanation is that the tumor produces a substance which inhibits biochemical processes in nerves. Occult carcinoma should be considered when the cause of a neurologic syndrome is not evident.

It is well recognized that carcinoma of the lung metastasizes to the nervous system with a high degree of preference. Estimates vary but approximately 30 percent of patients dying of carcinoma of the lung may have intracerebral metastases. Only metastases to lymph nodes, liver and adrenals are as frequent or more frequent. Central nervous system metastases may occur in the form of single or multiple discrete nodules or as leptomeningeal infiltration, that is, leptomeningeal carcinomatosis. In the leptomeningeal form, the clinical picture may simulate a chronic meningitis, with stiff neck, headache and cranial nerve and cerebellar signs. There may be cells in the spinal fluid. The sugar content of the cerebrospinal fluid is often lowered, making the differential diagnosis from tuberculous or yeast meningitis difficult.

However, the association of carcinoma of the lung or other malignant states with various neurologic syndromes, *in the absence of metastasis to the central nervous system,* is less well recognized. With rare exceptions, little attention has been focused on this unusual relationship during the past several years.

The neurologic syndromes associated with such malignancies fall into fairly discrete anatomic groups in that the presenting signs and symptoms primarily involve the cerebrum, cerebellum, spinal cord, peripheral nerves or muscles. A classification is shown in *Table 1*. There is often overlap, with features fitting into two or sometimes more of the above groups. This is particularly true of the polyneuritic type but the same may also be said of the cerebellar and spinal cord syndromes. Thus, the underlying process which results in injury to the nervous system is not completely specific regarding its site. In a given patient, however, one area will usually be more affected than others. The peripheral nerves and cerebellum appear most vulnerable and these syndromes are best recognized.

TABLE 1.

Neurologic Syndromes Associated with Malignant States

A. Cerebral
 1. Organic mental syndrome
 a. Depression
 b. Acute and chronic psychoses
 2. Progressive multifocal leukoencephalopathy

B. Cerebellar
 1. Parenchymatous degeneration (subacute cortical degeneration)
 2. Granular layer degeneration

C. Spinal cord
 1. Posterior column degeneration
 2. Amyotrophic lateral sclerosis syndrome
 3. Posterolateral degeneration

D. Peripheral nerve
 1. Polyneuropathy
 2. Guillain-Barré syndrome

E. Muscle
 1. Dermatomyositis
 2. Myasthenic syndrome

Cerebral Syndromes

Mental syndromes have long been recognized as occasionally accompanying other neurologic syndromes associated with carcinoma of the lung. However, a pure mental disorder may occur alone—without other nervous system signs and in the absence of metastatic disease to the brain. The presenting picture may be that of depression with insomnia, loss of appetite, psychomotor retardation or other stigmata of the depressive reaction. Or there may be intellectual impairment, variable in degree and fluctuating in its course. Alterations in the state of consciousness and even paranoid delusions have been seen. In most instances, the symptoms referable to the nervous system precede those of the primary system by two to six months. To date, carcinoma of the lung is the most frequent malignancy although other malignancies may also produce psychotic states.

The cerebrospinal fluid may show a mild increase in protein. No pathologic changes in the brain can be found to account for the clinical picture. Multiple sections show either no change or only minimal subependymal and white matter gliosis with chromatolysis of ganglion cells. The pathogenesis of this process therefore remains obscure.

The history of the following patient illustrates an organic mental syndrome with carcinoma of the lung. (Not shown)

Neuropathologic changes are absent in most patients. However, another neurologic syndrome, multifocal, leukoencephalopathy, usually in association with leukemia but also with Hodgkin's sarcoma, has been described. This is characterized by multiple areas of degeneration in the white matter of the brain and characteristic changes in the astrocytes.

Cerebellar Syndromes

The syndrome of subacute parenchymatous cerebellar degeneration is not as exclusively associated with carcinoma of the lung as is the cerebral type. It has been described in ovarian, breast, uterine and gastrointestinal carcinomas as well. This syndrome has been appreciated for a longer period than any of the others. In 1933, Parker described a patient with subacute parenchymatous cerebellar degeneration in association with carcinoma of the ovary. In 1934, Greenfield described a case of bronchogenic carcinoma associated with subacute cortical cerebellar degeneration. After these original reports, little additional material was added until 1951, when Brain reported three cases. Since then, there have been scattered reports describing this syndrome with malignancies of organs other than the lung. Brain and Henson made a comprehensive review of the subject in 1958. It seems, then, that this is not an uncommon syndrome and will be discovered more frequently once physicians are alerted to its existence.

The clinical features are those of cerebellar disease in general. The predominant features are ataxia and incoordination, particularly in the lower extremeties, with vertigo and nystagmus, running a fulminating downhill course unless modified by treatment. The neurologic syndrome often precedes the diagnosis of carcinoma.

Elevated protein with values from 65 to 140 mg. percent may be found in the cerebrospinal fluid. The cerebrospinal fluid cell count may also be elevated.

The salient pathologic features include widespread atrophy with degeneration of Purkinje cells. There is little degeneration of the neurons of the granular cell layer and no appreciable damage to the basket cells or tangential fibers. These changes are diffuse, involving the vermis as well as the hemispheres. There is often concomitant demyelinization of afferent cerebellar fibers in the cord and inferior peduncles.

Carcinoma with selective degeneration of the granular layer and preservation of the Purkinje cells has also been seen. None of these patients, however, demonstrate overt clinical cerebellar signs. This would seem to represent a separate process from the subacute parenchymatous cerebellar degeneration.

The following case history illustrates the syndrome of cerebellar disease in a patient with carcinoma of the prostate. (Not shown)

Spinal Cord Syndromes

Lesions of the spinal cord associated with extracerebral carcinoma have been reported. Changes have been described in the anterior horns and posterior columns. While these syndromes are considered exceedingly rare, the high incidence of carcinoma (10 percent) in patients with amyotrophic lateral sclerosis indicates that a possible relationship is ignored.

The most vulnerable areas are the posterior columns, usually in association with peripheral neuropathy. The two cases reported below are of interest because such cases may be confused with recognized neurologic entities, amyotrophic lateral sclerosis and combined system disease. (Not shown)

Peripheral Nerve Syndromes

In 1948, Denny-Brown and, concurrently, Wyburn-Mason called attention to the association of bronchogenic carcinoma with peripheral neuropathy, predominantly sensory in type. A number of case reports followed.

Peripheral neuropathies have been observed less frequently in association with carcinomas other than those of the lung. Dodgson and Hoffman reported a sensory neuropathy associated with carcinoma of the esophagus. Croft described a case which seemed related to adenocarcinoma of the colon and a second case related to prostatic carcinoma. However, no autopsies were performed and metastatic disease could not be excluded. Turner observed one patient with a malignant thymoma and another with neuropathy associated with a postcricoid carcinoma. In these instances, pathologic material was not available.

Victor reported five cases of peripheral neuropathy associated with multiple myeloma, in the absence of local myelomatous and amyloid deposits, which microscopically resembled the neuropathy associated with carcinoma of the lung. The patients presented with a symmetric, atrophic, areflexic, sensorimotor type of neuropathy.

The number of reports of peripheral nerve involvement is in sharp contrast to the few reports of mental and cord involvement and exceeds those of cerebellar involvement also. It appears predominantly in males. The type of neuropathy may be purely sensory or purely motor but more often there are varying shades of sensory and motor combinations.

In many patients, the symptoms of the neuropathy clearly antedate any symptom referable to the carcinoma (ranging from two to 42 months). In the presence of any unexplained peripheral neuropathy, carcinoma of the lung should be considered and included in the differential diagnosis.

The cerebrospinal fluid may be abnormal. The abnormalities usually consist of elevated protein or cell count. The pathologic changes within the peripheral nervous system, regardless of the tumor type, are characterized by demyelination and degeneration of the posterior root ganglia. All components of the reflex arc may be involved, either singly or in various combinations.

Guillain-Barré Syndrome

The association of carcinoma of the lung with an acute ascending paralysis of the Guillain-Barré type has been recorded on two occasions in the literature. A third such patient is described who was admitted with the diagnosis of an acute infectious polyneuropathy but who was later found to have a bronchogenic carcinoma. The neurologic picture cleared dramatically after removal of the tumor.

Discussion

The sensitivity of the central and peripheral nervous systems to the presence of carcinomas, myelomas and possibly other malignancies which have not metastasized to these areas seems to be similar to the sensitivity of the blood elements. Anemias, increase in sedimentation rate and hypercoagulable states occur with carcinoma. These indicate changes either of cells, bone marrow or perhaps intermediate organs such as the liver and are not the result of metastasis to the bone marrow or liver.

The mechanism of such damage to the central nervous system is obscure. Various explanations have been offered but none has been completely substantiated. Their very number indicates the dissatisfaction with which each has been received and the need for a more acceptable answer. Denny-Brown's original proposal seems most logical, namely, that the tumor releases a substance which competes with or inhibits an enzyme or coenzyme system which is necessary to maintain the integrity of myelin and neurons. The particular sensitivity of the peripheral nerves and cerebellum suggests that the inhibition may be in thiamine metabolism, specifically a defect in cocarboxylase. This is further suggested by the not uncommon excellent response to vitamin B administration. The occurrence of these neurologic lesions in association with a variety of malignant states suggests that this response is not tumor specific.

The presence of an occult carcinoma should thus be considered in any neurologic syndrome in which the etiology is not evident.

(The case histories that are not shown may be read in the original article.)

HYPERTHYROIDISM AND THYROID CANCER

Else Olen MD and G. H. Klinck MD, Washington, D.C. *Archives of Pathology 81(6): 531–535, June 1966.* *Copyright 1966 by American Medical Association.*

Opinions concerning the coexistence of hyperthyroidism and thyroid cancer are undergoing revision. In a study of the thyroid gland in hyperthyroidism made by Graham in 1941, there is no mention of thyroid cancer. Reports made since 1947 indicate that thyroid cancer has been found in as many as 5% of persons with thyrotoxicosis. The differences in the reported frequency of coexisting thyroid cancer and thyrotoxicosis might be explained by the criteria used for judging the presence or absence of hyperthyroidism. In addition, the diagnosis of cancer depends in part on the thoroughness of the gross examination of thyroid tissue and in part on the histologic interpretation of equivocal lesions. These problems are illustrated by comparing two reports involving cases prior to 1936, the era before the use of thiourea and related compounds. Crile reported two thyroid cancers (0.8%) among 249 cases of hyperthyroidism, whereas Hare and Salzman reported 16 thyroid cancers (8%) among 198 cases of hyperthyroidism.

Many of the reports relating to the coexistence of thyroid cancer and hyperthyroidism concerned patients upon whom operations were performed primarily because of a mass in the thyroid. These patients were in a sense "selected" by the physicians who had seen them prior to operation. Study of a series of thyroids removed primarily because of overactivity of the thyroid seemed to offer a good opportunity to determine the incidence of thyroid cancer in thyrotoxicosis. If the simultaneous occurrence of the two conditions is frequent enough to exclude coincidental occurrence, it would support the concept of a common etiologic factor.

Material and Observations

Histologic sections of portions of 2,114 thyroid glands from patients who had exhibited hyperthyroidism were studied for evidence of cancer. We included only those cases in which clinical evidence of thyrotoxicosis was confirmed by laboratory data or in which the patients had received antithyroid medication. This report is confined to material received at the Armed Forces Institute of Pathology (AFIP) from 1945 through 1963. The files of the AFIP include case material from the military, Veterans Administration, and civilian sources.

The material received prior to the use of antithyroid compounds in 1943 for the management of thyrotoxicosis was not included in this study, but 150 cases received at the AFIP prior to 1943 were reviewed, and one associated cancer was found. The tumor was an occult sclerosing carcinoma that had been interpreted at the time as a papillary adenoma. No conclusions were drawn from this limited review because of the comparatively small number of cases.

In the material used for this study, the majority of patients had received preoperative treatment with propylthiouracil and iodine or methimazole and iodine. A small number had received radioactive iodine only.

Among the 2,114 cases studied, 53 patients showed associated thyroid cancer; this is an incidence of 2.5% in the population of cases at the Armed Forces Institute of Pathology. The true incidence in the general population might be less than 2.5% because some of the AFIP cases were probably contributed primarily because of the presence of cancer. Forty-two of the cancers were found in toxic diffuse goiters and 11 in toxic nodular goiters. Three of the 53 thyroids contained a small follicular adenoma in addition to the cancer. Convincing evidence that any of these carcinomas originated in preexisting adenomas was not observed. Twenty-seven of the 53 were of a type frequently designated as "occult sclerosing carcinoma" of the thyroid. A typical example is shown in Fig. 1. Eighteen of the remaining 26 carcinomas were papillary, five were follicular, and three were poorly differentiated. Examples of these are illustrated in Fig. 2 to 4. Four of the 53 tumors were associated with metastasis

to regional lymph nodes. One of these was an occult sclerosing carcinoma, thus confirming the ability of this tumor to metastasize. Two of the four metastasizing carcinomas were papillary; one was an occult sclerosing carcinoma, and one was a poorly differentiated neoplasm. In the latter case, metastatic lesions in regional lymph nodes were discovered seven years after the first thyroid operation. Nine of the 53 thyroid carcinomas associated with hyperthyroidism showed intrathyroidal spread or were of multifocal origin. Fifty-one of the 53 specimens were surgically removed; two were encountered at necropsy. In both autopsy cases, the cause of death was not related to the thyroid cancer. Distant metastasis was not observed in any of the cases. Although the available clinical information was usually sparse, the majority of these thyroid cancers were not suspected clinically and were found only on examination by a pathologist. This is not surprising, because more than one half of the thyroid carcinomas were of the occult sclerosing type, hence usually less than 1 cm in diameter.

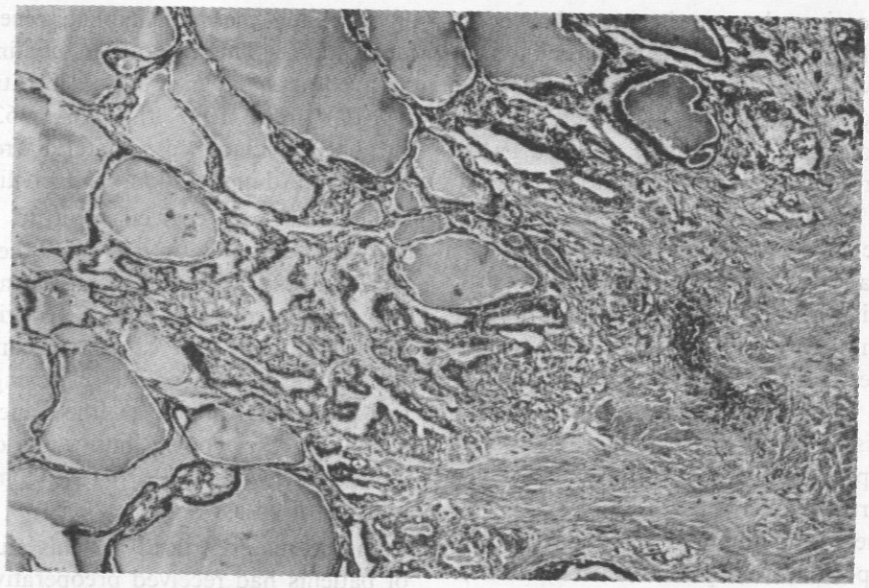


Fig. 1.—Occult sclerosing carcinoma. A portion of the periphery of the lesion showing the central focus of sclerosis and the junction between tumor cells and adjacent thyroid follicles (AFIP negative 65–2020, X 75).

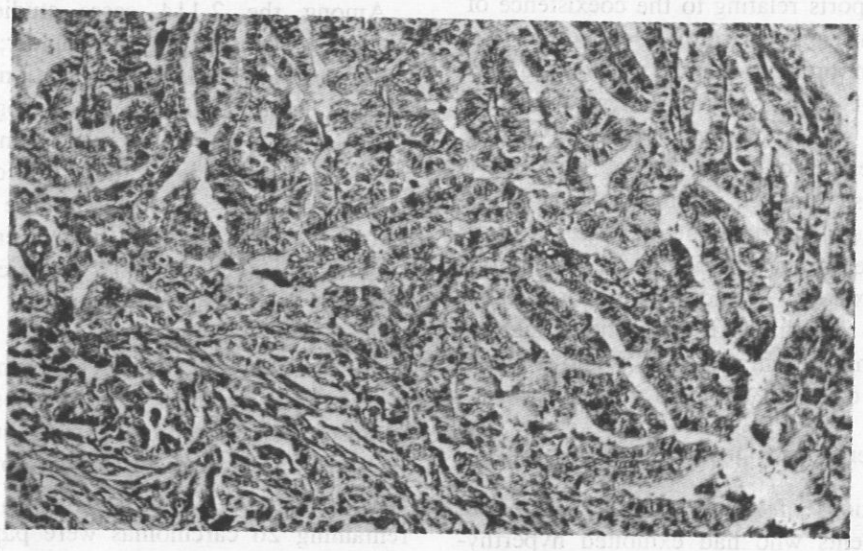


Fig. 2.—Papillary carcinoma. Small portions of this tumor were composed of well-formed papillae, but most of the lesion displayed only rudimentary papillary formations (AFIP negative 65–2018, X 50).

The age ranged between 16 years and 68 years, the majority of the patients being in early middle age. There was a similar age distribution of thyrotoxicosis. Among the 53 patients with hyperthyroidism and an associated thyroid cancer, 39 were women and 14 men, a ratio of about three to one. Because of the predominantly male population of the hospitals contributing to the AFIP, conclusions as to distribution by sex should not be drawn.

Comment

The search for associated thyroid cancers in AFIP material among patients with evidence of hyperthyroidism revealed an incidence of 2.5%. Although this incidence is not high, it supports the current idea that there might be some common background for the two conditions. This seems plausible because thyroid epithelial hyperplasia is dependent on thyrotropic hormone, and cancer can

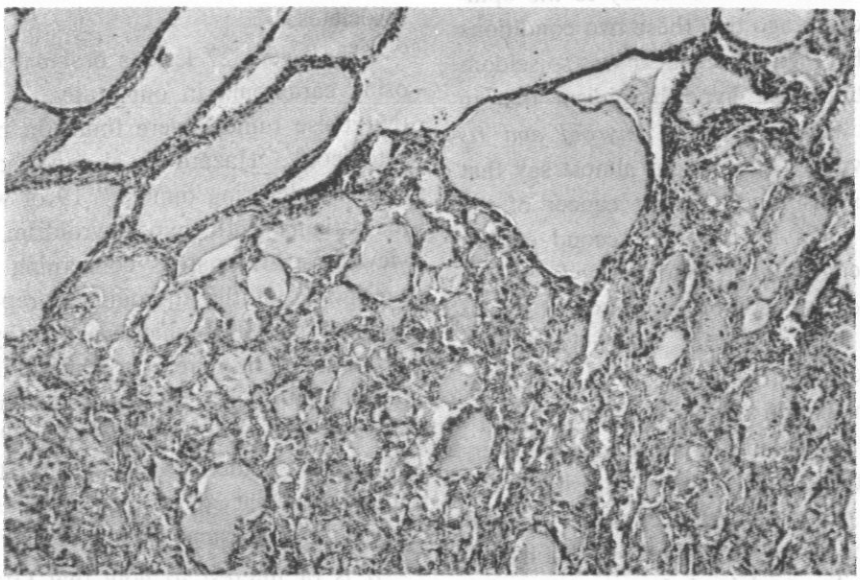


Fig. 3.—Follicular carcinoma. This tumor was composed of some well-defined follicles, but in most places follicle formation was poor (AFIP negative 65–4926, X 80).

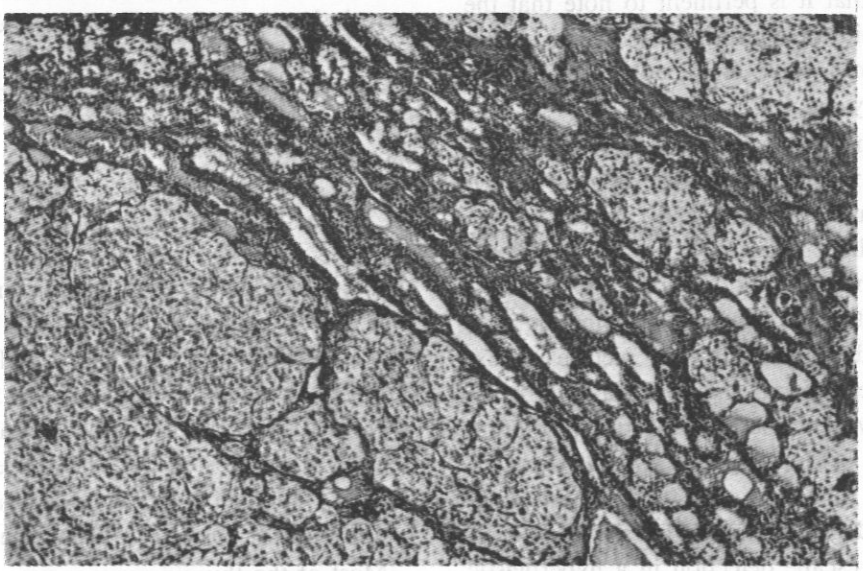


Fig. 4.—Poorly differentiated carcinoma. Most of the lesion was composed of solid masses of cells with only a suggestion of follicle formation, but in a few places well-developed follicles were present. There was also a minute focus of papillary formation (AFIP negative 65–2022, X 80).

be produced in the rat thyroid by inducing the production of large amounts of thyrotropin. For a time these tumors are endocrine dependent in that they stop growing, or even regress, if the pituitary output of thyrotropic hormone is suppressed. Recognition of this led to the use of thyroid hormone to depress the release of thyrotropic hormone from the pituitary in patients with thyroid cancer.

The discovery of 53 thyroid cancers among 2,114 patients with thyrotoxicosis is contrary to the opinion held a few decades ago that these two conditions rarely occur together. Thyroid cancer was so seldom found in association with hyperthyroidism that in 1937 in the first edition of *The Thyroid and Its Diseases* Means wrote: "One might almost say that thyrotoxicosis was insurance against cancer of the thyroid." Eleven years later in the second edition of this book, Means and Rawson stated: "Since publication of the first edition we have observed five patients who had cancer of the thyroid associated with thyrotoxicosis."

Is there an explanation of this apparent discrepancy? An actual increase in thyroid cancer in hyperthyroidism has little factual support. Holsinger and Stevens suggested that the apparent recent rise in the incidence of coexisting thyroid cancer and hyperthyroidism might be explained by an increasing awareness of the association of the two conditions and a more careful pathologic study of the resected glands. We feel that it is pertinent to note that the very small thyroid neoplasms now called occult sclerosis carcinomas were frequently classified as benign in earlier years.

There are some points of histologic similarity among untreated toxic goiters, toxic goiters treated with thiouracil, and some thyroid cancers of the follicular or papillary type. The similar histologic appearances of these conditions might have made pathologists reluctant to diagnose carcinoma in a toxic goiter. Today the histologic picture of extreme or bizarre thyroid hyperplasia in thyrotoxicosis is rarely seen because of the involution induced by iodine before surgery. A focus of papillary carcinoma is relatively easy to detect histologically in a thyroid gland that is the site of involution, but it might escape detection in a hyperplastic gland.

In our 2,114 cases of hyperthyroidism the incidence of thyroid cancer is 2.5%. This does not differ significantly from the 2.8% (28 cancers) found by Mortensen et al in their meticulous examination of thyroid glands from 1,000 consecutive routine autopsies. These subjects were largely elderly individuals in whom a higher incidence of cancer might have been expected than in our group of mostly younger subjects. On the other hand, the sampling of the thyroids in our series cannot be compared to the extremely detailed examination of the thyroids in the series studied by Mortensen and associates.

There were 27 lesions designated as occult sclerosing carcinoma in our study. It should be noted that these tumors were found in patients with thyrotoxicosis. Hazard et al reported 25 "nonencapsulated sclerosing tumors," 19 of which were found in patients with hyperthyroidism. Zettergren reviewed several papers concerning occult sclerosing carcinoma of the thyroid and reported six tumors of this type, all of which were in thyrotoxic subjects. One should be careful to differentiate between diffusely hyperplastic thyroid glands and thyroid glands associated with thyrotoxicosis. This distinction is not always made clear in the literature. We wish to emphasize that all of the thyroids studied in the present report came from thyrotoxic individuals.

It is of interest to note that Graham first called attention to the lesion now usually called occult sclerosing carcinoma as "adenocarcinoma not arising in adenoma." He did not state whether the lesions were in hyperplastic thyroids or whether the patients had evidence of thyrotoxicosis, but he did state that "malignancy rarely if ever develops in the hypertrophic and hyperplastic thyroids associated with exophthalmic goiter."

Summary

The histologic sections of portions of 2,114 thyroid glands from patients exhibiting hyperthyroidism were studied at the Armed Forces Institute of Pathology for evidence of cancer. In 53 instances, an associated cancer was found. The incidence of 2.5% in this material supports the current opinion that the association of hyperthyroidism and thyroid cancer is frequent enough to be of clinical significance.

Most of the thyroid cancers were small, and more than one half were of the occult sclerosing type, thus less than 1 cm in diameter. Eighteen were papillary carcinomas, five were follicular, and three were

poorly differentiated carcinomas. Forty-two of the cancers were in diffuse toxic goiters and 11 in nodular toxic goiters. In only four patients had carcinoma spread to regional lymph nodes. Metastasis to distant sites was not observed. Only a few of the tumors were suspected clinically. All patients were treated preoperatively with propylthiouracil and iodine or methimazole and iodine, except two who had received ^{131}I. Thirty-nine were female patients and 14, male.

This study shows that the older concept of "cancer being almost unknown in exophthalmic goiters" is not valid and that the two conditions do occur together. (The references may be seen in the original article.)

CARING FOR THE PATIENT—A THRICE-TOLD TALE*

Alex M. Burgess MD† and Alex M. Burgess, Jr. MD‡, Province, R. I., and Boston, Mass. *New Eng J Med 274(22): 1241–1244, June 2, 1966.*

For some patients, though conscious that their condition is perilous, recover their health simply through their contentment with the goodness of the physician. (Hippocrates, Precepts, Chapter 6.)

From the earliest times the importance of the physician himself as a force in the treatment of the patient has been recognized by thoughtful people. Indeed, until recent times one could say that this was his greatest, and at times his only, contribution to the recovery of his patient. The more new and effective tools he is given to work with, the greater his possibilities of positive accomplishment, and the greater his chance of misusing his newfound powers and of losing his older, and still important ones.

As medical care becomes more complex, both in technics and in organization, and as the hospital assumes an increasingly central role in diagnosis and treatment, the systems and routines necessary to regulate the diagnostic and therapeutic machinery, and the swarm of professional and subprofessional personnel that operate it, emerge. Necessary as they are, they carry with them the tendency to replace sympathetic concern with system, and constructive thought with unimaginative routine.

Needless to say, it is not our purpose to belittle the magnificent consequences of modern scientific medical achievement, but rather to sound a cautionary note. As with ancient morphine, or modern atomic energy, all the tools of medicine must be used with regulated enthusiasm and judicious restraint. More important still, they must be used in the light of a real appreciation of human values. Although the word "iatrogenic" has recently come into common use, the concept is old, and in accenting the seamy side of medical care, one can claim no originality. This sort of warning must be sounded many times in every generation if it is to be kept firmly in mind.

The value of the time-honored principle "nil nocere" was well illustrated in the last century by the success of homeopathy. The harmless dilutions and the childlike faith in them, shared by both physician and patient, resulted in many recoveries that might have been delayed by the use of the potent and potentially harmful medication commonly employed by the regular profession.

How does the physician become a pathogen? It may be by omission or commission—that is, he may fail to do the right thing, he may do the wrong thing, or he may do both. He may transgress in diagnosis or in treatment, and may err with his knife, his drugs, his actions or his attitudes. Murphy's law, the origins of which are shrouded in mystery, states, "If a mistake is possible, someone will make it," and it is safe to say that mistakes will continue to be made. A few recurring errors in medical management that seem frequent enough to constitute trends have been noted, however. Most of them are preventable with only a little thought. We have

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selected a few examples with no pretense of covering the whole field of iatrogenic disease.

Contact with medical care always carries with it a greater or less risk. We hope and believe that it is a small one, and well justified by the anticipated gains. The responsibility for keeping the risks small and the gains great rests upon the physician. In the United States, in 1960, death occurred as a result of the complications of medical or surgical procedures to about 6 persons per 1,000,000 population (fractionally higher for the nonwhite population), and according to the National Health Survey's check of a national sample, 7.8 people out of 1,000 reported accidents due to "therapeutic misadventure" during the year beginning July 1, 1959. We should emphasize the fact that in all probability none of the cases reported in this communication would have been counted in such statistics, being subtle and, we fear, more frequent.

In discussing harm that may occur to a patient receiving modern medical care, we do no intend to include errors that may be inevitable if the physician has not acquired the skill and judgment that may be considered standard for the doctor who has had adequate medical-school training and hospital experience. Nor shall we discuss damage to a patient as the direct result of the action of a doctor who has decided on proper grounds that the risk of such an outcome should be accepted. We shall, however, consider as "iatrogenic" and worthy of the attention of the profession such errors of omission or commission as may be directly or indirectly caused by able physicians acting in accordance with modern medical usage. These may, in some cases, be due to lack of skills or experience that have not been sufficiently emphasized in the training received in medical school and hospital. Others are the result of situations over which the physician has no control—for example, the necessity of hospitalizing patients who could be better cared for at home except that nursing care and simple laboratory examinations are not now as available outside the hospital as they were a few decades ago.

Unnecessary Hospitalization

It may be recalled at the outset that today's physician faces many pressures that urge the hospitalization of the patient. Family patterns and homes frequently do not provide facilities adaptable to the care of the sick as they once did, and domestic help, as well as home nursing service, continues to become more and more difficult to find. Furthermore, with the growth of hospitalization insurance, the patient can often better afford the things he needs in the hospital than outside. Indeed, with the increasing complexity of technology and apparatus, what few diagnostic procedures are now available outside are often inferior. Then too, even in some cases in which the physician could quite properly handle situations himself, he tends to fall into the habit of leaning on the hospital house staff, if his hospital is fortunate enough to have one, since this allows him to make a fully acceptable contribution to the patient's care with less personal effort.

Hospitalization is not, however, a favorable matter, other things being equal, and there are risks of cross-infections and the multiplication of possibilities of error based on the involvement of many persons in the care of the patient. Other things, however, are usually not "equal," and these risks very often must be accepted, but every effort should be made to minimize them. With full realization of the value of the essential diagnostic and therapeutic facilities offered by hospitals, it is pertinent to point out some of the disadvantages that should be considered when hospitalization is recommended. Harm to a patient occurring during the hospital stay may to some degree be considered iatrogenic if the hospitalization could properly have been avoided. The following case is an illustration furnished to us by Dr. Jay M. Orson.

A 1½-year-old boy suffered a fall in which his head struck the pavement. He did not appear severely hurt, but x-ray examination disclosed a linear, nondepressed fracture, about 4 cm in length, in the parietal region. Although there were no abnormal signs or symptoms he was hospitalized for 5 days. On the 5th day pneumonia due to a resistant strain of staphylococcus developed, and he was desperately ill but recovered.

In the hospital the patient is served by many employees, some of whom may not be as well trained as others. For example, there have been reports of several cases of gastric rupture by oropharyngeal insufflation of oxygen through a carelessly inserted nasal catheter, not equipped with a stop disk, which had penetrated the esophagus.

Multiple Laboratory Procedures

A profusion of data may lead to confusion of diagnosis. When one is presented with a difficult diagnostic problem the present-day procedure too often is the accumulation of a mass of data, most of it consisting of multiple laboratory determinations, and then an attempt to put the facts together like a

picture puzzle and read the answer. This is well illustrated by a clinicopathological conference, carried on by a very able clinician and his service. The presentation included laboratory data covering a large blackboard. The patient had died without a definite diagnosis after very careful study by well informed and intelligent young people. To several physicians who were attending the conference and who had not attempted to evaluate the profusion of laboratory tests, the history, physical findings and course of illness appeared to point clearly to liver abscess, and the post-mortem examination showed that there was indeed such an abscess, resulting from pylephlebitis. Possibly, an early and correct diagnosis would have resulted in successful treatment.

In a second case it was stated, after exhaustive laboratory investigation, that no diagnosis could be made, but it seemed clear to perhaps less sophisticated hearers that the history, symptoms and signs and the course of the illness indicated necrotizing pancreatitis, and that was what was found. One of the older men remarked in the discussion that followed, "If, sixty years ago, Dr. Reginald Heber Fitz had seen these 2 patients, he would, in each case, have made a correct diagnosis in fifteen minutes." Essential and important as they are, sometimes the results of multiple laboratory tests constitute the trees that tend to obscure the forest.

Unquestioning acceptance of x-ray reports often leads to misdiagnosis. This is no fault of the radiologist, who reports what he sees and leaves it up to the clinician to make proper use of the information that he furnishes. This is illustrated by the following cases:

A 22-year-old Negro entered the hospital with a history of malaise, weakness, diffuse muscle pains and chills in the evening for 7 days. The temperature varied between normal and 105°F., reaching 102°F. or higher every afternoon or evening. The white-cell count varied between 5,600 and 7,900 with a relatively high percentage of lymphocytes. X-ray examination showed infiltration of the lower portion of the left upper lobe, which was considered by the radiologist as probably a pneumonitis of virus origin. Although the fever continued for 12 days, the service was unwilling to consider tuberculous pneumonia. Finally, antituberculosis medication was applied, and the temperature fell to 101°F. or lower, by rectum, for 3 days and then to normal. On the 30th hospital day the cultures from the sputum and gastric washings were positive for tubercle bacilli. In this case the x-ray interpretation was considered sufficient evidence against tuberculosis to delay treatment for almost 2 weeks.

In another case the suggestion of the radiologist that tuberculosis should be considered, despite the lack of fever or a clinical picture suggesting the disease, led to the use of antituberculosis medication in a patient a biopsy of whose lung eventually showed anaplastic carcinoma cells infiltrating pulmonary lymphatics.

The Maze of Modern Medication

Probably the commonest unfavorable results of the physician's efforts are those that involve the use of drugs, especially new ones. When a new type of medication is developed, it is recommended for use on the basis of its demonstrated favorable action. Unfortunately, it often takes a relatively long time for evidence of unfavorable results to be recognized and documented. The dramatic case of thalidomide furnishes a striking example. Practically every medication that is capable of favorable action if properly administered is also potentially dangerous, a fact that, despite the most rigidly controlled clinical trials, may not come to light until it has been in use for months. All this is well known but deserves emphasis. The widespread use of corticosteroids comes to mind. Only recently has the medical profession been able to determine when and when not to use these products and how long it is wise to continue them. Many other important drugs have been discredited after enthusiastic overuse and have had to be reevaluated in the light of their disadvantages before their place as truly valuable agents is determined.

Antibiotics, with their wonderful record of control of infections, can, as we all know, have serious or fatal consequences. The chance of superinfection by resistant organisms is a risk that must be accepted when the situation is so serious that there is no time for identification of the infecting organism, but unless this is the case it is the duty of the physician to determine if possible what he is treating before antibiotics are given. Although this is well understood, the commonest error in present-day practice is probably the misuse of these agents. When a patient insists on penicillin for a cold or influenza, for example, it is difficult to refuse to give it, but if staphylococcal pneumonia later develops, the physician is to blame, for he has taken a chance with his too easy willingness to please. As well understood by the profession as is the risk of superinfection when antibiotics are used, unfortunately some laymen, on the basis of a popular misapprehension, bring pressure to bear on

the physician to take action that he knows, or should know, is not in the patient's best interest.

Modern therapy, including as it does many subcutaneous, intramuscular and intravenous injections of various sorts, involves many risks and requires accurate supervision. Fortunately, severe damage is rare because the risks are well known. Nevertheless, pulmonary edema from too rapid intravenous infusion, for example, does occur. The use of complicated technics and apparatus, often lifesaving, requires careful training. Accidents still occasionally occur. In other cases associated with modern therapy, procedures whose effects have only recently been brought to light can be mentioned. Examples are the increased tendency to the development of malignant tumors that has been shown to result from radiation of the thymus in babies and the appearance of retrolental fibroplasia that has followed the use of relatively high concentrations of oxygen in the care of premature infants.

The History and Physical Examination

Many of the old virtues seem to be neglected or lost. As a result of the mass of technical information that students and house officers are supposed to absorb, a breed of physicians who are capable medical scientists but poor doctors is coming into existence. Evidence of this is seen almost daily on ward rounds. When an attending physician who can quote the literature with great accuracy can diagnose by a clumsy physical examination an extensive pleural effusion that does not exist or misses a nodular liver that is easily palpable 4 cm below the right costal margin, something is wrong. The same thing is true when the staff of a distinguished clinic can fail to make a diagnosis after many days of study and several hundred dollars' worth of laboratory procedures because an incomplete history did not point to a diagnosis that was clearly evident when a proper history had been obtained. The substitution of multiple testing for a carefully taken history and adequate physical examination is one of the great sources of diagnostic confusion.

Fully as important are the unfortunate consequences of failure to understand patients as people rather than as cases of abnormal physiology and biochemistry. The discussion of symptoms and signs in the hearing of the patient in terms that he fails to understand but that cause him acute apprehension has, from ancient times, been recognized as a sin, but it is a sin that is frequently committed.

An example is found in the case of a young woman in her thirties hospitalized for a major psychoneurotic condition necessitating removal from her family environment for many weeks. During her hospital stay it became evident to her psychiatrist that she was becoming extremely anxious about her heart. Under the logical supposition that a negative report from a cardiologist would strengthen his hand, he sent her to a colleague, who in time did report entirely normal findings. However, while fluoroscoping the patient, he allowed himself to say, "Let me see, you said you had not had rheumatic fever, didn't you?" Despite his negative final report and the protestations of all concerned, the remark cost the patient, in the opinion of the psychiatrist, a delay of no less than six months in her return to normal activities.

The statement that "we should not treat diseases but people" is often quoted and much more often disregarded. When one tells students and house officers, "At times what you say to patients is more important than what you do for them, and it may be more damaging to say the wrong thing than to give the wrong medication," one is telling a truth that all practicing physicians have had to learn.

Success in this important phase of therapy is the result of the development of a real golden-rule policy by the physician. When he has developed the essential habit of trying to find out just what the patient is feeling and fearing—in other words to imagine himself in the patient's situation, anxieties and worries included—he will be able to avoid everything disturbing and to build up the patient's morale. As Charcot said, "The best inspirer of hope is the best physician."

Summary and Conclusions

With full appreciation of the great advances that medicine has made and is making, it has been our plan to call attention to some of the defects that result in less than optimum patient care. As in many types of progress there is also a simultaneous retrogression, fortunately of relatively small magnitude but nevertheless of real importance. In taking three or four steps forward, we are also perhaps taking a step or two backward. Our purpose in this communication has been to emphasize these backward steps.

We have pointed out some of the risks of hospitalization, usually small compared to the advantages of treatment in a hospital, but yet recognizable and to a great extent correctable. We have discussed the overemphasis on multiple laboratory examinations that has at times been allowed to outweigh clinical

judgment based on a carefully taken history and adequate physical examination. We have mentioned some of the many examples in which a new medication has had apparent early success followed by evidence of later damage that has modified the indications for its use or even caused it to be abandoned. Finally, we have stressed the apparent loss of skill in the fundamental arts of history taking and carrying out the physical examination, and the tendency to forget that the patient is a person, not a case—a human being whose personality should be studied, whose fears and worries comprehended and whose morale in facing his disease and all that it means to him must be maintained.

The decline of interest on the part of the physician in personal family practice is a pressing problem and tends to relegate him to a relatively technical and impersonal position. The patient, with his burden of fears and anxieties, is the loser. As one eminent man expressed it, "We patients prefer a bit of humble attention to the most distinguished neglect." With the development of great numbers of specific laboratory tests and of many predictably effective forms of therapy, the physician faces an almost irresistible temptation to practice a brand of medicine that overlooks the central role of his human sympathy and wise judgment in addition to his technical skills. The physician of fifty years ago had, in many situations, only himself to offer, and though incomparably less effective in terminating certain diseases, notably the infections, he knew how to throw his weight into the balance on the patient's side. There is nothing in today's advances that need prevent us from emulating him.

(The references may be seen in the original article.)

NEW USES FOR AN OLD HORMONE

Herbert A. Selenkow MD and Marvin S. Wool MD**, Clin Pharmocol Ther 7(4): 564–566, July-August 1966, The C. V. Mosby Company, St. Louis.*

Hypothyroidism is no longer a rare disease. Widespread therapeutic use of radioactive iodine has increased the incidence of progressive thyroid failure to unexpected proportions, and this insidious complication has necessitated critical reappraisal of isotopic therapy for hyperthyroidism. In view of the recognized deleterious effects of hypothyroidism and the well-known diffculties and delays attendant on its diagnosis, some observations on prevention of thyroid insufficiency by the administration of thyroid hormones seem justifiable and timely. The indiscriminate or injudicious use of thyroid hormone therapy as a metabolic cure-all is to be deplored. However, under circumstances which are known to produce a high incidence of thyroid insufficiency, for example, following radioactive iodine therapy or subtotal thyroidectomy for lymphoid thyroiditis, selective use of full therapeutic doses of thyroid hormones to prevent hypothyroidism is indicated.

From the physician's viewpoint, hypothyroidism of brief duration is not usually associated with irreversible or permanent disability and once detected, is, fortunately, fully correctable. To the patient, however, it is an insidious, distressing, and debilitating disorder which is inconsistent with optimal health, vitality, and productivity. In the elderly, cerebrovascular, respiratory, and cardiac effects superimposed upon preexisting degenerative disease may be life threatening or fatal. Unfortunately, the detrimental effects of thyroid insufficiency are not confined to the elderly. In the young, it may result in retardation of growth, development, and maturation.

During the reproductive years, unrecognized hypothyroidism may adversely affect menstruation, libido, fertility, and conception. An adequate supply of thyroid hormone is also important during the physiologic "stress" of pregnancy, since limitation of maternal thyroid secretion at critical stages of gestation may be detrimental to fetal development and, perhaps, even to fetal survival. This vital role of thyroid hormones in the successful conducts of pregnancy is well known. At any age, myxedema, the ultimate stage of hypothyroidism, is associated with even more pernicious effects and more profound pathologic alterations. Despite its potential virulence, however, it is relatively common for this disorder to develop in a subtly progressive manner with misleading symptoms. The correct diagnosis is often not apparent until extensive and costly examinations have excluded other diseases.

There are several situations where hypothyroidism can be anticipated and, thus, thyroid replacement instituted early to prevent hypothyroidism. The most common of these occurs following administration of radioactive iodine for hyperthyroidism. The progressively high incidence of hypothyroidism has been emphasized recently by Dunn and Chapman who reported a 20 percent incidence 2 years after this therapy, and a 40 percent cumulative occurrence at 10 years. This complication is apparently not related exclusively to dosage, to technique of administration,

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or to adjunctive measures, but results, at least in part, from additional unpredictable characteristics of each patient. Development of hyperthyroidism is now the major disadvantage of this otherwise remarkably effective therapy and must not be permitted to limit its use, particularly since thyroid insufficiency can be anticipated and obviated. Although the incidence of hypothyroidism following subtotal thyroidectomy for hyperthyroidism is lower than that following radioiodine, it is nonetheless a significant complication. For this reason, most patients treated for hyperthyroidism by isotopic radiation as well as by surgical ablation must be followed carefully and for prolonged periods to detect early signs of thyroid insufficiency.

In this clinic it has been our policy, in 500 patients treated with radioactive iodine during the past 10 years, to institute thyroid replacement at the earliest indicated time. Patients selected for this preventive measure include those in whom hyperthyroidism responds rapidly to radioactive iodine, and those whose clinical status and laboratory tests of thyroid function (particularly the serum protein-bound iodine) fall to low normal levels within 3 to 6 months after therapy. Thyroid hormone replacement is similarly given to patients in whom even transient hypothyroidism would be undesirable, such as in young women in the reproductive years and in the elderly. These patients are given 120 to 180 mg desiccated thyroid or its equivalent in synthetic hormones. Preventive thyroid therapy has also been used in combination with antithyroid drugs for treatment of hyperthyroidism and in chronic lymphoid thyroiditis (Hashimoto's struma) which predisposes to a high incidence of hypothyroidism.

The simple expedient of taking thyroid in full replacement doses has the obvious advantage of avoiding development of hypothyroidism. In addition, it provides a physiologic milieu for growth and development as well as for conception and gestation without concern for thyroid insufficiency or limited thyroid reserve. It permits prognostic assessment of thyroid function in patients previously treated for hyperthyroidism through a continuous "suppression test." It limits the number of bothersome and costly periodic examinations to detect early development of hypothyroidism. Finally, since there is evidence that hypothyroidism aggravates the ophthalmopathy of Graves' disease, thyroid replacement provides a stable environment to permit its regression.

Preventive thyroid therapy used properly is gaining increasing support. The slight cost and minor inconvenience of taking one tablet daily to prevent the undesirable effects of this complication are certainly justified. Thyroid hormones are remarkably safe; there have been no significant adverse drug reactions in over 75 years of common usage, and iatrogenic hyperthyroidism does not occur with physiologic dosages.

Thyroid hormone therapy is not a panacea. Its use to prevent hypothyroidism is no substitute for periodic follow-up examinations or good medical care. However, the many benefits of early thyroid therapy in clinical situations that predispose to a high incidence of thyroid gland failure more than justify the practice.

(The references may be seen in the original article.)

MEDICAL ABSTRACTS

DRUG DEPENDENCE

WHO Chronicle 20(2): 65–67, Feb 1966.

The terms "drug addiction" and "drug habituation" are often used improperly or considered as synonyms. "Addiction" is commonly applied to any misuse of drugs for nonmedical purposes, with the connotation that serious harm is involved for the individual and society. This rather wide application can only create confusion and misunderstanding. After careful consideration, a WHO Expert Committee accordingly recommended the substitution of the term "drug dependence" for "drug addiction" or "drug habituation". This term does not carry any implication of risk to public health or of need for a particular type of control.

"Dependence" is defined as "a state arising from repeated administration of a drug on a periodic or continuous basis". It is essential to specify the type of drug involved in each particular case. The characteristics and the social and economic repercussions of this phenomenon should also be borne in mind. These vary according to the type of drug, and the harm caused to the individual and society is determined by the type of dependence.

In general, drugs having a stimulating or calming effect on the central nervous system may produce a "psychic dependence". Certain of them provoke a "physical dependence" manifested as an "abstinence syndrome" when their effects are interrupted by withdrawal or by administration of a specific antagonist. Many dependence-producing drugs also induce a "tolerance" characterized by a diminished response to the drug and the need to increase doses in order to produce the same degree of pharmaco-dynamic effect. Drugs that are capable of inducing dependence may also be associated with psycho-toxic effects that are manifested by profound alterations in behaviour. These effects may occur with a single large dose or in the course of continued administration, or they may be precipitated by withdrawal of the drug following continued administration. The pattern of abnormal behavior is, within limits, characteristic for each drug type, but individual responses vary widely, depending, among other things, on the preexisting mental state of the person involved.

Characteristics of drug dependence

A recent paper in the *Bulletin of the World Health Organization,* describes 7 different types of dependence. These are:

Morphine type

(a) Strong psychic dependence in the form of an overpowering drive or compulsion to continue taking the drug and to obtain it by any means, for pleasure or to avoid discomfort.

(b) An early development of physical dependence which increases in intensity, paralleling increases in dosage. This requires continued administration of the same drug, or an allied one, to maintain a semblance of homeostasis and to prevent the appearance of the symptoms and signs of withdrawal. Withdrawal of the drug or administration of a specific antagonist precipitates a definite, characteristic, and self-limited abstinence syndrome.

(c) Development of tolerance that requires an increase in dosage to obtain the initial pharmaco-dynamic effects.

Barbiturate-alcohol type

(a) Psychic dependence of varying degree that may lead to periodic rather than continuous abuse, especially with alcohol.

(b) The definite development of a physical dependence that generally, however, can be detected only after the consumption of amounts considerably above the usual therapeutic or socially acceptable levels. When intake is reduced below a critical level, a characteristic self-limited abstinence syndrome ensues, the symptoms of which, in the case of barbiturates, can be suppressed not only by a barbiturate-like agent but also, at least partially, by alcohol. In the case of alcohol, the situation is reversed.

(c) The development of tolerance which is irregular and incomplete, so that there is considerable persistence of behavioral disturbance dependent upon the pharmaco-dynamic effects of the drugs. There is a mutual, but incomplete, cross-tolerance between alcohol and the barbiturates.

(d) Alcoholism frequently has overt pathological effects on the tissues, but such effects have not been shown to occur with the barbiturates.

Cocaine type

(a) Strong psychic dependence.

(b) No development of physical dependence and absence of a characteristic abstinence syndrome when the drug is withdrawn.

(c) Absence of tolerance; rather, there is sensitization to the drug's effects in some instances.

(d) A strong tendency towards continued administration, as in coca-leaf chewing, or rapid repetition of the dose, as in the current practice of intravenous administration. Quantitatively, the effects are strikingly different, according to the mode of abuse.

Cannabis (marihuana) type

(a) Moderate to strong psychic dependence according to the desired subjective effects.

(b) Absence of physical dependence, so that there is no characteristic abstinence syndrome when the drug is discontinued.

(c) Little tendency to increase the dose and no evidence of tolerance.

Amphetamine type

(a) A variable psychic dependence.

(b) No physical dependence and, consequently, no characteristic abstinence syndrome, though withdrawal will be followed by a state of mental and physical depression as the organism escapes from the persistent stimulation.

(c) The slow development of a considerable degree of tolerance to many effects, though not all components of the cerebral system participate equally

in this, so that nervousness and sleeplessness persist and psychotoxic effects such as hallucinations and delusions may occur.

Khat type

Khat dependence of the traditional type, i.e., when the drug is ingested by chewing the leaf, has the following characteristics:

(a) Moderate but often persistent pyschic dependence as long as its maintenance is at all practicable.

(b) Lack of physical dependence.

(c) Absence of tolerance.

Hallucinogen (LSD) type

Psychic dependence on drugs of the LSD type varies greatly, but it is usually not intense. No evidence of physical dependence can be detected when the drugs are withdrawn abruptly. A high degree of tolerance to LSD and to psilocybin develops rapidly and disappears equally rapidly. Tolerance to mescaline develops more slowly. Persons who have tolerance to any of these 3 drugs are cross-tolerant to the other two.

Six-Point Control Plan for Sedatives and Stimulants

Concern about the abuse of sedatives and stimulants was expressed by the Eighteenth World Health Assembly. In the latest report of the WHO Expert Committee on Dependence-Producing Drugs, six measures are recommended to combat "the epidemic-like spreading of this abuse, particularly among young persons in certain countries". These are:

(1) availability of the drugs on medical prescription only;

(2) full accounting of all transactions from production to retail distribution;

(3) licensing of all producers;

(4) limitation of trade to authorized persons;

(5) prohibition of non-authorized possession; and

(6) establishment of an import-export authorization system.

There must be control of the flow of the materials into and out of the country.

The Committee used the terms "sedatives" and "stimulants" to designate any drugs that have been found to be dependence-producing and shown to be abused because of their sedative or stimulant effects on the central nervous system. Alcohol and substances under international control were excluded from this definition.—PrevMed Div, BuMed.

RESULTS OF WATER FLUORIDATION IN CHILE

Kotlik, A. R., Obregon, J. J., and Fiegehem, L. B., Bulletin of the Pan-American San Office 59(3): 212–220, Sept. 1965.

The paper deals with the effects of the application of an optimal concentration (1 p. p. m.) of fluoride to drinking water in the city of Curico, Chile, for the past 11 years. An examination was made of the permanent teeth of the school population (6–15 age group) in Curico, and the results compared with a control group of similar characteristics of sex and socioeconomic status in the city of San Fernando, Chile.

The results indicated the advisability of adding this optimal concentration of fluoride to drinking water. Essentially, the results of the test were the same as those obtained in other countries. The preventive action of fluoride was verified as follows:

(a) The DMF index of the schoolchildren in Curico was considerably lower than that of the similar group in San Fernando. Children who had been drinking fluoridated water all their life (6–11 age group) had a reduction rate of 55.3%, while the older children (12–15 age group), who had not enjoyed this benefit all their life, had a reduction rate of 45.1%.

(b) The DMF index reduction could be verified from every aspect, and was greater for tooth decay and loss.

(c) There was an appreciable difference in the number of children free from caries: 29.11% in Curico; 7.74% in San Fernando.

(d) There was also a marked difference in the caries rate of the first molar: 33.46% without first molar caries in Curico, and 9.27% in San Fernando. First molar loss in San Fernando was over twice that loss in Curico.

(e) Less than 8% of the schoolchildren in Curico had fluorosis, and it in no case affected their appearance.

It is therefore considered that water fluoridation is justified, as is the national program of prevention of dental caries which the Dental Section of the General Department of National Health Services in Chile is sponsoring.—PrevMed Div, BuMed.

DENTAL SECTION

INTERACTION OF LASER RADIATION WITH ORAL HARD TISSUES

Lohene, R. R. and Fine, S. J Pros Den 16(3): 589–597, May-June 1966.

Based on this study, the authors observed that the disadvantages and unknowns portend a long period of research before the laser beam will be useful to dentistry. Extracted human teeth with sound enamel were exposed to laser radiation at a wavelength of 6934 Å, and exit beam energy levels of 12 and 25 joules. Focused and defocused beams were used. The lens system provided spot sizes of 0.1 and 0.3 mm D, resulting in calculated energy densities of 10^4–10^5 joules per cm^2 per pulse at the point of impact. The duration of impact was approximately 1 millisecond per pulse. The gross specimens showed a crater which varied in size with the laser beam intensity, and the surrounding area appeared chalky white with a glasslike fusion of the surface enamel. In sections through the crater, the adjacent enamel showed a zone of disrupted enamel rods which extended from the apex of the crater to the D-E junction, seen both in white and polarized light. Enamel exposed to 25 joules laser beam produced an X-ray diffraction identical to normal enamel. Knoop Hardness Numbers of lased enamel were similar to normal. A thermocouple in the pulp chamber indicated an 80–90° C temperature rise from 25 joule laser irradiation of the labial enamel surface; but for technical reasons this was considered equivocal.

EFFECT OF A CHILLED COOLANT ON THE HUMAN PULP DURING CAVITY PREPARATION

Croft, L. and Stanley, H. R., Oral Surg, Oral Med and Oral Path 22(1): 66–71, July 1966.

Recent histopathologic studies have shown the biologic advantages of using adequate water coolants to reduce pulpal response. In this study, intentionally cooled water was used in the air-water spray to determine whether the inflammatory response to the cavity preparation was altered in any way.

Fifty-seven vital, non-carious teeth which were to be extracted for periodontal or prosthetic reasons were used. Typical Class V cavity preparations were cut, under local anesthesia, with a Number 37 inverted cone diamond at 20,000 rpm with intermittent cutting pressure. The procedure was carried out under copious amounts of water (20.5 cc per minute).

The temperature of the air-water spray at the bur was measured just prior to cutting of the preparation and after completion of the preparation, and an average temperature determined. When the reservoir water was chilled to 33.8°F–39.2°F, the temperature of the air-water spray at the bur ranged between 54.4°F and 64.4°F. However, when the reservoir water was 72°F, the temperature at the bur was 64.4°F.

After cavity preparation, the teeth were filled with zinc oxide and eugenol and extracted under general anesthesia at intervals of 24 hours to 16 days. They were fixed, decalcified, and processed by standard methods. These specimens were grouped according to the temperature of the coolant at the cavity preparation. Thirty-five specimens were prepared with the coolant between 54.5°F and 57.6°F, and twelve were prepared with the coolant between 62.6°F and 64.4°F. A control group of ten was prepared at 64.4°F.

Microscopic comparisons between the three groups were made by recording the incidence and intensity of cellular displacement, the inflammatory response in the superficial and deeper pulpal tissues, and the number of specimens predominating in leukocytes. No significant histopathologic differences between the three groups were noted. On the other hand, there appeared to be no significant detrimental effects in terms of pulpal response when an exceptionally cooled water coolant was employed. (Abstracted by CDR W. B. Gregory, Jr. DC USN, U. S. Naval Academy, Annapolis, Md.)

PERSONNEL AND PROFESSIONAL NOTES

AWARDS AND COMMENDATIONS. CAPT F. S. Wozniak DC USN was recently awarded the Navy Commendation Medal for meritorious service while serving with the First Force Dental Company, First Marine Division, during deployment to Okinawa and the Republic of Vietnam. The presentation was

made by Major General A. R. Kier USMC, Acting Commanding General, Fleet Marine Force, Pacific, in the name of the Secretary of the Navy.

Chief Dental Technician K. L. Walls USN, was commended in the name of the Secretary of the Navy by Major General A. R. Kier, Acting Commanding General, Fleet Marine Force, Pacific. Chief Walls' commendation was for outstanding achievement in the superior performance of his duties while serving with the Third Dental Company, Headquarters Battalion, Third Marine Division deployed in the Republic of Vietnam.

OCCUPATIONAL MEDICINE SECTION

ARE YOU A DEFENSIVE DRIVER?

The Health Bulletin, April 1966.

Are you a defensive driver? Check out these questions below and see if you qualify:

1. Do you often make fast stops? The defensive driver seldom, if ever, has to "hit his brakes". He stays alert to the situation ahead and slows in advance. Quick stops indicate a failure to foresee trouble and plan to avoid it.

2. Do you have close calls at intersections? The defensive driver doesn't. He approaches each intersection prepared to deal with sudden changes in the traffic pattern and unexpected actions by other drivers.

3. Do you have to brake on curves and when turning corners? The defensive driver doesn't. He eases up on his motor and slows before reaching the turn.

4. Do you have to "hit the brakes" when the driver ahead of you stops short? The defensive driver doesn't. He always stays far enough back so that he can slow down easily if the car ahead stops short.

5. Do you glide past cars that are stopped preparing to turn? The defensive driver doesn't. He passes with caution, aware that the stopped driver may change his mind, or that there may be a pedestrian in front of the stopped car.

6. Do you make fast starts? The defensive driver doesn't. He always starts easily so that he is prepared for a sudden change in circumstances.

Do you check out as a defensive driver? If not, it's time to review your present driving methods. If you don't you may be greatly increasing chances that you will be involved in a serious traffic accident.

MERCURY VAPOR EXPOSURE

Occupational Health in the States, Division of Occupational Health, Public Health Service, Department of Health, Education and Welfare.

In an industrial plant a mercury thermostat heat regulating device located inside an oven, which was used to heat metal parts, ruptured and the estimated 600°F. temperature of the oven vaporized most of the mercury into the plant air.

The oven was located in a small unoccupied room at the end of a large machine shop. Mercury vapor from the oven was circulated throughout the machine shop area exposing nine workers for several hours to concentrations of mercury vapor estimated to be near 5.0 mg/m^3 air. Six men were hospitalized, two others were under medical care, and one man returned to work the following day with apparently no ill effects. The exposed men had symptoms primarily of lung irritation and chest X-rays indicated pneumonitis or pulmonary edema.

Within twelve hours the machine shop and adjoining office areas were ventilated from Hg vapor. The room containing the oven was decontaminated, closed off from the rest of the plant, and ventilated for forty-eight hours which reduced airborne Hg vapor to less than .04 mg/m^3 air.

This unusual incident points out that acute exposures to high mercury vapor concentrations result in pulmonary effects rather than in the well-known systemic effects caused by the more common chronic exposures to lower vapor concentrations.

MORE ABOUT SMALL CARS

H. Gene Miller, Manager, National Safety Council's Statistics Department, Traffic Safety, October 1965.

In the April issue of Traffic Safety, NSC's chief statistician summarized the special studies that have been made regarding small-car accidents. The principal findings of that summary were: (1) that small cars apparently are not involved in accidents any more frequently than large cars, and (2) when accidents do happen, the occupant fatality rate for small cars is about twice as high as the rate for large cars.

This follow-up analysis traces the increase in the number of small cars during the last half dozen years, and shows what impact this increase has had on the total motor vehicle death count.

The number of occupant deaths in small cars in accidents totalled about one-fourth of all motor-vehicle occupant deaths in 1964, compared with less than 10 percent in 1960, and only about 3 percent in 1958. Between 1958 and 1964 the number of occupant deaths in standard-sized passenger cars ("large") cars was about unchanged (23,400 in 1958 and 23,500 in 1964), but the number of occupant deaths in small cars increased from about 800 to 8,000.

What is the basis for these statistics? First, a summary of the studies of small-car accidents *(Traffic Safety,* April 1965) which indicated that, although the *accident* rate for small passenger cars apparently is not different from the rate for large passenger cars, the fatality rate *in accidents* is about twice as high for the small cars; and second, that the number of small cars as a percent of the total passenger car population has increased from about 1.8 percent in 1958 to nearly 17 percent in 1964.

The table shows the number of domestic small cars (compacts) produced, and the number of cars imported since 1958 *(Automobile Facts and Figures,* 1965). The imports are presumed to be mostly small passenger cars. Also shown in the table are the indicated yearly totals, using a 10-year car life, and the percentage of small cars in the total passenger car population by years.

Foreign small cars in 1964 were about one-third of the small-car total, and domestic compacts about two-thirds. In most of those states studying small-car accidents, the foreign cars and domestic cars were considered as a group, and the findings were related to the entire group. Only California made separate tabulations of the foreign small cars, which they labeled "economy," and the domestic small cars, which they labeled "compact." The tabulations showed that casualties per accident in the economy cars were somewhat higher than in the compacts, and

Small Passenger Cars vs Large Passenger Cars[1]—Numbers, Occupant Death Rates, and Deaths
Total United States by Years

	1958		1959		1960		1961		1962		1963		1964		1964[5]	
Foreign cars																
Annual new imports	431[2]		668		444		279		375		409		516			
10 year moving total		1,004		1,665		2,089		2,344		2,686		3,066		3,547		
Domestic (compacts)																
Annual production	0		0		1,317		1,426		1,604		1,980		2,126			
Cumulative total		0		0		1,317		2,743		4,347		6,327		8,453		
	%		%		%		%		%		%		%		%	
Total small cars	1.8	1,004	2.8	1,665	5.5	3,406	8.0	5,087	11.6	7,033	13.6	9,393	16.7	12,000	1.8	1,300
Total large cars	98.2	55,866	97.2	57,897	94.5	58,153	92.0	58,173	88.4	59,043	86.4	59,634	83.3	59,864	98.2	70,564
Total passenger cars	100	56,870	100	59,562	100	61,559	100	63,260	100	66,076	100	69,027	100	71,864	100	71,864
Death rates[3]																
Small cars[4]		8.2		8.0		7.6		7.2		7.4		7.4		7.6		7.6
Large cars		4.1		4.0		3.8		3.6		3.7		3.7		3.8		3.8
All passenger cars		4.3		4.2		4.0		3.9		4.1		4.2		4.4		4.4
Occupant deaths in:	%		%		%		%		%		%		%		%	
Small cars	3	800	5	1,300	10	2,400	14	3,400	17	4,600	21	6,200	25	8,000	4	1,000
Large cars	97	23,400	95	23,500	90	22,200	86	21,300	83	22,200	79	22,700	75	23,500	96	27,000
All passenger cars	100	24,200	100	24,800	100	24,600	100	24,700	100	26,800	100	28,900	100	31,500	100	28,000
Total MV deaths[6]		36,981		37,910		38,137		38,091		40,804		43,564		47,700		44,200

[1] "Small" includes foreign small cars and domestic compact cars; "large" includes all other passenger cars.
[2] All vehicle totals in thousands.
[3] Occupant deaths per 10,000 passenger cars.
[4] Small-car rate set at twice the rate for large cars on the basis of special studies.
[5] Based on 1964 rates and 1958 proportions of small cars and large cars.
[6] Including occupant deaths in trucks and other vehicles, pedestrians, bicyclists, motorcyclists, other.

for each group of small cars, casualties were nearly double those for large cars, despite lower average car occupancy of the small cars.

The death rates shown in the table (occupant deaths per 10,000 passenger vehicles) are based on numbers of vehicles, and use a two-to-one ratio indicated by the small-car studies in general. (A study in Maine showed that small-car casualties were five and one-half times large-car casualties.) As noted, the occupant death rates for both the small cars and large cars were only a little higher in 1964 than they were in the immediately preceding years, they were the same in 1960, and they were lower than in the years before that. However, the increasing proportion of small cars, with their higher death rate, has pushed the total occupant death rate up 13 percent since 1961. Stated another way, the 1964 occupant death rates for both small cars and large cars were close to the lowest on record, but the changing "mix" of the passenger car population contributed to the sharp rise in death rates since 1961.

The last column in the table shows that, if the number of small cars in 1964 had remained at 1.8 percent of the total passenger car population as they were in 1958, and if the total number of vehicles had still increased to the present count (87.3 million in 1964), deaths would have been about 3,500 less than that actually occurred. These figures indicate that about one-third of the sharp rise in motor-vehicle deaths in recent years has been due to the increase in the number of small cars with their higher occupancy death rates.

THE FOURTH DIMENSION IN OCCUPATIONAL HEALTH

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The opinions or assertions contained herein are the private ones of the authors and are not to be construed as reflecting the views of the Navy Department or the naval service at large.

As we move into the increasing complexities of our modern scientific age, we encounter with almost dismaying frequency innovations and modifications in the environment which may have direct effects on the health of the population. These changes range from those as basic as nuclear energy to those as effete as new packaging methods or materials. Those of us in industry are faced with the evolution of new materials, processes and products, each of which presents its own modification of environmental factors which may have an effect on the health of employees or, in some cases, the consumers or the community. Those of us in the armed services have seen the development of new weapons systems that, aside from their efficacy in dealing with an enemy, also pose health hazards to the personnel required to use and service them.

As is the case with so many of the facets of today's civilization, the total field of endeavor of occupational health becomes complex and more sophisticated as time passes. For centuries occupational medicine was concerned almost exclusively with the treatment of the ills and injuries of man which arise out of or during the course of his occupation. Johnstone and Miller identify three phases of development of occupational health[1]: (1) The accident and safety phase in which the concern was almost wholly with traumatic surgery and compensation medicine; (2) The Occupational disease and industrial hygiene phase, and (3) The present broad preventive or health conservation phase.

It is probable that none of us has advanced completely into this third phase and that most of us are in the period of transition into the preventive phase. The success of this treatment is dependent in large part upon the successful application of what we have termed the fourth dimension in occupational health.

The accomplishment of the task of the conservation of health in industry is dependent upon the success of the health team in four areas of preventive medicine. First of these is the recognition, the second is evaluation and the third is the control of environmental causes and sources of illness in industry. Most of us recognize these as the cardinal requisites of industrial hygiene. These are the physical dimensions, the length, width, and breadth of occupational health. It is probable that most programs can be considered as successful if judged by these measurements alone. However, without the successful application of the fourth dimension, communication, oc-

cupational health becomes a mere intellectual exercise of considerable interest to those engaged in the field but of negligible value to those who are meant to be its beneficiaries.

A brief consideration of the first three is in order before taking up this fourth dimension.

The *recognition of environmental* hazards in the occupations of man has been of historical interest. Industrial medicine certainly is not young. Hippocrates described lead colic and noted the toxic properties of this metal. Calen, Agricola, Paracelsus and Herodotus wrote of the diseases peculiar to miners, tanners, chemists, soldiers and others. The monumental contributions of Ramazzini marked the true beginnings of occupational health as a formal discipline.

Most frequently in the past the identification of these hazards was accomplished ex post facto, that is upon the occurrence of clinical cases of disease. The etiological agent in the environment was identified and removed. Our more recent efforts have been better oriented toward the prevention of disease.

With the wealth of information available to the field of occupational health today, the problem of identification of hazards has, in most cases, been eliminated and it is possible to make a prior judgment of the hazard of environmental hazards before the occurrence of illness in the population at risk. This is well illustrated in a recent instance of Naval experience in which estimates of the hazards involved and recommendations for their control were made prior to the completion and deployment of Polaris firing submarines.

The *evaluation of the hazard* is the joint responsibility of industrial hygienist and physician. Once the existence of a hazard is established or suspected some evaluation of its degree is mandatory. This may be in the nature of direct measurements of environmental factors such as a dust particle count, a sound-pressure level reading, or a measurement of the concentration of a noxious chemical. Another means of evaluation of the hazard is by examination of exposed personnel by means of physical, x-ray, laboratory, audiometric or other appropriate examination procedures.

Control of environmental causes is accomplished by the application of engineering remedies to the environment when possible supplemented by the provision of personal protection to the employee when necessary.

It is quite possible that all of the prerequisites might be satisfactorily fulfilled and still, through failure in communication, not result in the final control of a health hazard. A recounting of such a case is carried in a recent publication.[2]

In 1601 a fleet of four ships of the East India Company sailed from England for the Indies. Sir James Lancaster, captain of one of the ships, was in command of the fleet. At this time the chief danger faced by marines on long voyages was scurvy, a disease of unknown cause or cure. When Lancaster reached port months later, the majority of his crew was hale and hearty. The other three vessels barely reached port and then only with the aid of Lancaster and his men. These other crews were decimated by scurvy. In all 105 deaths occurred due to this disease.

Lancaster was no physician, but when scurvy broke out among his crew, he promptly administered lemons to his men, the healthy as well as those who became ill. For the first time the prevention of scurvy by citrus fruits was recorded, but for some reason this knowledge was not disseminated.

It was not until 1795 that the Admiralty provided for organized measures for the prevention of scurvy at sea. Meanwhile, it is said that one million deaths occurred from scurvy, due to this failure in communications.

Patty [3] refers to the modern aluminum foundry in which the designer provided extremely poor ventilation. This flaw was due to his failure to appreciate well-known principles of ventilation practices. The cost of correcting this defect exceeded the original cost of the ventilation system.

Although Hippocrates and other ancient writers knew of the dangers of working with lead, yet as late as the 1920's lead poisoning was not an uncommon occupational disease among painters. Lead had been identified as an environmental hazard for literally thousands of years, general knowledge of its toxicity was available, and the means of control existed. Yet cases continued to occur. Why? Although there were other factors, the primary failure was that those who knew the hazards of lead and how to control them failed to communicate with those who had a need to know.

I am sure that you can add to a list of such failures from your own experience in your own specialty.

The United States Navy like any other large and complex organization is faced with certain inherent problems in communications. The Navy is one of the largest employers of industrial manpower. Currently more than 340,000 civilian employees and thousands of sailors are engaged in virtually the entire

spectrum of occupations ranging from clerical to the heavy industry of Navy shipyards as well as the operation of the most modern, sophisticated weapons.

Daily in the Navy thousands of our personnel are exposed to environmental agents capable of affecting their health if uncontrolled. The task of identifying and evaluating these agents that confront our personnel in their daily work is indeed a formidable one. For the new health hazards presented by the recent advances, we have available the cooperation and guidance of other government agencies, the universities and industry. For the control of the "old" hazards we have the benefit of our own experience and accumulated wealth of knowledge stored in the literature.

An equal or perhaps greater challenge is the need to get this information to top management, to supervision, and to the men doing the work. An effective administrative program has developed to cope with this challenge.

At the departmental level this communication exists between the Occupational Health Division of the Bureau of Medicine and Surgery and appropriate divisions of the various management bureaus. Communication must start with the top management and from there proceed down the line to the men doing the work.

From departmental level, general guidelines on occupational health (such as threshold limit values) are issued world wide to the ships and the approximately 150 shore plants that comprise the Naval Establishment. One of the most effective techniques is to make safety an integral part of the job itself. The Bureau of Medicine and Surgery is consulted whenever a new job technique is under development to advise on the safety measures that will be necessary to protect the men doing the job.

A pitfall before all of us in preventive medicine is becoming enamored with the new and exotic. We are inclined to forget that the old and familiar, which if ignored, is nonetheless hazardous. The importance of a sustained program of education which not only stresses the new, but reiterates the old, cannot be overemphasized.

In reviewing statistics on the principal causes of disability among Federal employees, it is not surprising to find that the first three causes are: (1) handling material and equipment; (2) falls of persons; (3) striking against material. What is surprising is to find that the fourth most common cause of disability is (you would never guess it either) "dog-bite".

Navy people in the field of Occupational Health should not permit themselves the luxury of any feeling of superiority over their colleagues in the Post Office Department whose employees not surprisingly were almost the sole sufferers of this indignity. After all, the Navy has been able to apply the fourth dimension with humans, but I doubt that even a tough bos'n mate could communicate with a dog.

It is generally recognized that the Navy's occupational health service is comparable to the best in government and private industry. A comprehensive review of the administrative framework of this program would show that success is largely due to the recognition of the fourth dimension of occupational health—communication.

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EDITORIAL DESK

CONGRATULATIONS ON THE 124TH ANNIVERSARY OF THE NAVY MEDICAL DEPARTMENT

Personally and on behalf of the United States Marine Corps, I wish to extend hearty congratulations and best wishes on the 124th anniversary of the founding of the Navy Medical Department.

As you know, I recently returned from a visit to Navy and Marine units in Vietnam and I cannot commend your people highly enough for their valor under fire, their immediate care and attention to our wounded, and their firm help with our civic action program in that torn country. The unit commanders I saw and the wounded Marines I visited throughout the West Pac area spoke nothing but praise for the devoted medical personnel who served them.

With warm regards and best wishes,

Sincerely,

s/Wallace M. Greene, Jr.

General, U.S. Marine Corps

TRI-SERVICE OB-GYN SEMINAR

The 15th annual Armed Forces Obstetric and Gynecologic Seminar will be held at Fitzsimons

Army General Hospital, Denver, Colorado, on 23 to 27 October, 1966. This year's host will be the Army with LCOL George P. Foley, (MQUSA), Chief of Ob-Gyn Service, serving as Program chairman. The meeting will incorporate professional papers on timely subjects together with panel and round table discussions. In addition, there will be a number of participating civilian consultants.

Requests to attend the seminar should be submitted in accordance with BUMED Instruction 1520.8A. A government airlift is anticipated provided that participation warrants its use.

Housing facilities promise to be very adequate with some 180 rooms available at the BOQ and Officers Club. Requests for registration forms, and other inquiries should be directed to George F. Foley, LCOL (MC) USA, Chief, Obstetrics and Gynecology, Fitzsimons General Hospital, Denver, Colorado 80240.

SOCIETY HONORS ADMINISTRATOR OF LOCAL HOSPITAL

CDR Thomas L. Hollis MSC USN, Administrative Officer of the U.S. Naval Hospital San Diego, Calif., was advanced to Fellowship status in the American College of Hospital Administrators on August 28, in Chicago. CDR Hollis was the first active duty naval officer so honored.

The announcement was made by the ACHA President Boone Powell, Administrator of the Baylor University Medical Center in Dallas, Texas, who presided at the ceremony.

The ACHA is a professional society of men and women whose life's work is in the field of hospital administration. The membership comprises 6,900 administrators, assistant administrators and administrative assistants of hospitals in the United States and Canada.

The honor was accorded at the College's 32nd Annual Convocation ceremony which was held in the Arie Crown Theatre, McCormick Place. The Convocation preceded the annual meeting of the College, held in conjunction with the convention of the American Hospital Association.

CDR Hollis holds a Bachelor of Science degree from the University of California and a Masters of Hospital Administration degree from the University of Minnesota. He has served as a Preceptor for both the University of Minnesota's Program in Hospital Administration and the George Washington University's Program in Health Care Administration. Five Medical Service Corps officers have served their Administrative Residencies under CDR Hollis' preceptorship.

At the same event, the ACHA confered its highest commendation, Honorary Fellowship, upon five distinguished leaders in the hospital and health fields. They are: C. Wesley Eisele MD, Associate Dean, Post Graduate Medical Education, University of Colorado Medical Center, Denver; Marion B. Folsom, Former Executive Secretary, Department of Health, Education and Welfare, Washington; James E. Ludlam, Attorney—Partner of the Musick, Peeler and Garrett Law Firm, Los Angeles; Thomas L. Perkins, Chairman of the Trustees of the Duke Endowment, New York; and William I. Taylor MD, Executive Director, Canadian Council on Hospital Accreditation, Toronto.—American College of Hospital Administrators, Chicago, Ill.

MEDICAL PHOTOGRAPHERS GRADUATE

On 26 August 1966, NAVMEDSCOL's Medical Photography Class No. 9 graduated with a class average of 84.9. The Honorman, HM3 Robert L. Hershey, was awarded a letter of Commendation by the Acting Commanding Officer, CAPT J. J. Humes MC USN, for his exemplary scholastic achievement.—Public Affairs Office, NNMC, Bethesda, Md.

NAVAL MEDICAL SCHOOL PROVIDES TRAINING MATERIAL FOR VIETNAMESE

Late in March 1966, the U.S. Naval Medical School, National Naval Medical Center, Bethesda, Maryland, forwarded a supply of medical training material to the Veterans Administration, Boston, Massachusetts, for use in training Vietnamese Nurses and Corpsmen. The material was sent in response to a request by the Chief of the Medical Benefits Division, Veterans Administration Outpatient Clinic, Boston, Massachusetts for reference material and specific medical and technical publications in the fields of Physical Medicine, Clinical Laboratory, Roentgenology, and training courses utilizing "correspondence course" techniques. This material will be retained by the Vietnamese Medical Team upon their return to South Vietnam for further use in teaching other students.—Naval Training Bulletin, page 34, Summer, 1966.

NAVAL MEDICAL SCHOOL OFFICERS CITED FOR VOLUNTARY WORK IN MEDICAL SELF-HELP PROGRAM

In a ceremony held on 30 March 1966, CAPT J. H. Stover, Jr. MC USN, Commanding Officer, U.S. Naval Medical School, presented Medical Self-Help Instructor certificates to CAPT Gordon C. Bell MSC USN and to CDR Edmund H. Gleason MSC USN, both officers of his command. The certificates were presented on behalf of the Chief, Division of Health Mobilization, District of Columbia Department of Public Health, Mr. Hibbs S. Meek, in appreciation for the noteworthy contribution by CAPT Bell and CDR Gleason to the Medical Self-Help Training Program and to the community.

The Medical Self-Help course is designed to provide information and training to the people of the United States in preparation for survival in potential disasters when the services of a physician or other paramedical personnel are not available. The program includes sixteen hours of instruction in Radioactive Fallout and Shelter, Healthful Living in Emergencies, Artificial Respiration, Shock, Burns, Bleeding and Bandaging, Fractures and Splinting, Transportation of the Injured, Nursing Care of the Sick and Injured, Infant and Child Care, and Emergency Childbirth.—Public Affairs Office, NNMC, Bethesda, Md.

EDITOR'S NOTES

The association of nonmetastatic systemic diseases with cancer, while long recognized, has been the subject of an increasing number of articles in medical journals during the past several months. Modern interest in the occurrence of thrombophlebitis and carcinoma of the pancreas was stimulated by Sproul [1] in 1938, but she referred to Trousseau as one of the earliest observers to stress the coincidence of malignant tumors of epitherial origin and venous thrombosis (1865). In a review of the cases of thrombophlebitis and cancer seen in the vascular section of the Department of Medicine of the New York Hospital—Cornell University Medical College, Lieberman,[2] et al., describe the tendency of thrombophlebitis which appears in association with neoplasma to be recurrent or migratory and to appear in multiple extremities; and they state that it is resistant to anticoagulants; and accompanied by a increased risk of pulmonary embolism. In their series, thrombophlebitis occurred most frequently with carcinoma of the lung, female reproductive tract, and pancreas, but a wide variety of other cancer sites were encountered and they noted in their summary that thrombophlebitis may be the first sign of neoplasm.

Nonneoplastic cutaneous lesions with various forms of malignant disease were described by Weiner [3] and were the subject of an interesting scientific exhibit by Curth [4] at the Annual Meeting of the American Medical Association, 1954; those listed are: pruritis; urticaria; acquired ichthyosis; melanin spots of oral mucosa, lips, and digits; multiple cutaneous and subcutaneous "soft tumors"; pachydermoperiostosis; malignant ancanthosis nigricans; erythema multiforme; erythema gyratus repens; herpes zoster; dermatitis herpetiformes; lupus erythematosis; and unilateral nevi.

Knowles [5] et al., discussed extrapulmonary manifestations of bronchogenic carcinoma in 1955 and listed metabolic abnormalities: Cushing's syndrome, hypercalcemia, excessive antidiuretic hormone, and carcinoid syndrome; neuromuscular abnormalities: cortical cerebellor degeneration, peripheral neuropathy (sensory or sensimotor), dementia, and psychosis—mixed forms, and carcinomatous myopathy or polymyositis; connective-tissue and osseous abnormalities: clubbing and generalized hypertrophic osteoarthropathy, dermatomyositis, scleroderma, and acanthosis nigricans; vascular (endothelial) abnormalities: migratory thrombophlebitis, nonbacterial endocarditis; hematologic abnormalities: anemia—hemopathic hemolytic and symptomatic hemolytic, fibrinolytic purpura, and cryofibrinogenemia. The authors point out that none of these disorders are pathognomonic of bronchogenic carcinoma, all being found occasionally in association with other malignant tumors or even with debilitating diseases per se and that few of these syndromes can be explained adequately on the basis of current concepts of the metabolism of neoplastic tissue or can be related to any known function of normal respiratory epithelial cells.

"Extrathoracic Manifestations of Bronchogenic Carcinoma" is the title of a paper by Anderson & Bernatz.[6] They add myasthenic syndrome, serum protein abnormalities, polycythenima, renal sodium loss, and gynecomastia as additional manifestations.

The American Journal of Medicine,[7] 1964 includes, among its articles, a review of unusual manifestations associated with carcinoma and add leukemoid and leukoerythroblastic reactions, nonmetastatic hepatomegaly, Zollinger-Ellison and related syndromes, hyperglycemia and hypoglycemia, and they append a list of 140 references.

In January of this year, Morton [8] et al., reported 23 new cases of nonmetastatic neurological complications of bronchogenic carcinoma and reviewed 142 previously reported cases. The incidence of carcinomatous neuromyopathy associated with bronchogenic carcinoma was 14 percent in their series. Neurological symptoms preceded the diagnosis or initial symptoms of carcinoma in 83 percent of the patients in the combined series and 32 percent of these had neurological symptoms for one or more years before the appearance of symptoms or the diagnosis of carcinoma.

"Hypernephroma—The Internist's Tumor" is discussed by Kiely [9] and 11 case histories with a broad variety of disorders that may be found in patients having hypernephroma without metastases are presented. He feels that adequate roentgenographic study of the kidneys, even nephrotomography, if necessary, should be a part of the usual work-up of patients with obscure systemic diseases.

"Neuromyopathy in Cancer" is the title of a leading article in the *British Medical Journal* [10], March 12, 1966. As in some of the other articles, the possibility of toxins secreted by the tumors having a direct effect on the neuromuscular tissue is discussed but the fact that no such toxins have been found is reiterated. Furthermore, it is pointed out that there is no correlation between the size of the tumor and the degree of neural disorder. The possibility of some form of autoimmune reaction is noted as an attractive hypothesis and this is also mentioned by Lee, Yamanchi and Hopper ("Cancer and the Nephrotic Syndrome") in this issue of the News Letter.

In a recent report of a study of urinary hormone patterns in lung cancer and emphysema by Marmorston [11] et al., the patterns were found to be abnormal in these diseases. Actually, the abnormalities had a distinctive pattern for the various cell types of carcinoma studied (adeno, squamous, and anaplastic), and for emphysema. The authors feel that their findings suggest that the endocrine system is involved in lung cancer and in pulmonary emphysema and recommend expanding the number of metabolites studied so as to take account of additional components of the endocrine system, including thyroid and other pituitary factors. Previously, the same investigators [12] had reported that hormone excretion patterns in persons with breast and prostate cancer differ from those in persons without cancer.

The articles and reports emphasize that one or more of the associated syndromes may initiate the symptomatology of a malignant tumor and in this context, awareness of the possible significance of the syndrome may lead to earlier diagnosis and treatment of cancer than would be possible otherwise. Mention is made also of the possible remission of systemic symptoms after removal of the primary tumor.

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The American Journal of Surgery, Volume 112, Sept 1966, features a symposium on Diseases of the Liver.

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